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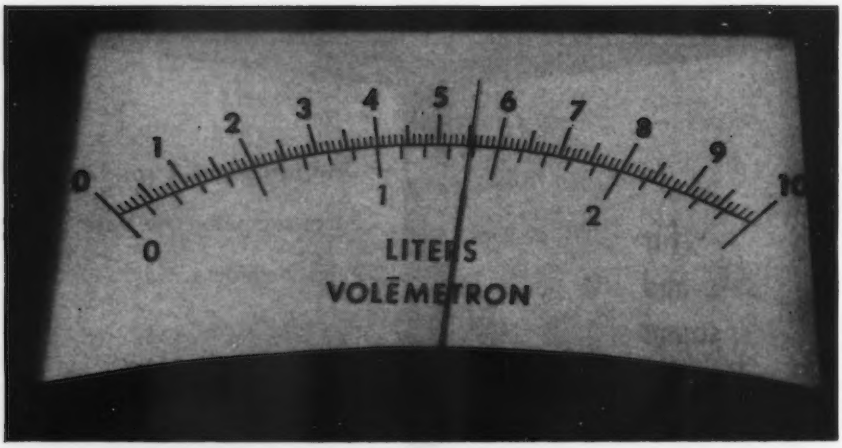

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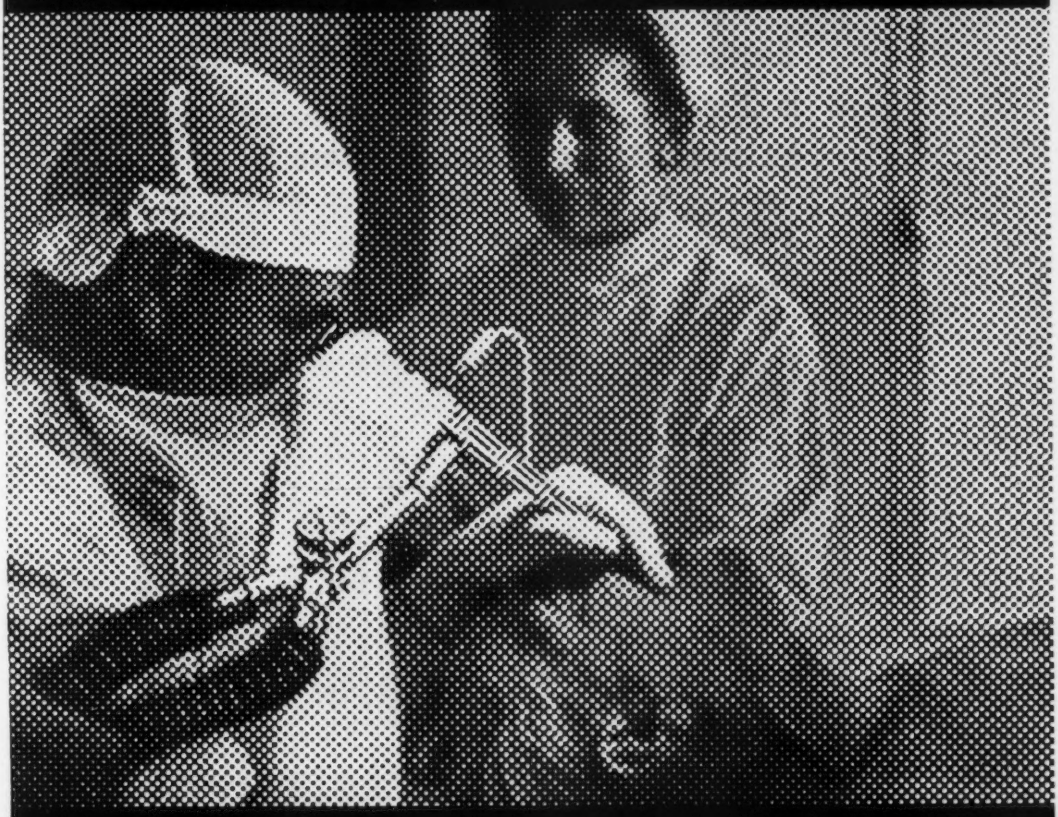

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*B. Sheiner, *C.A.M.J.*, *83*, 1377-78, 1960.

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CENTRAL EFFECTS OF FIVE MUSCLE RELAXANTS*†

LEWIS W. HERSEY, M.D., CHARLES W. GOWDEY, D.PHIL., AND WOLFGANG SPOEREL, M.D., F.R.C.P.(C.)‡

RESEARCH in the past twenty years has contributed significantly to the basic understanding and management of diverse problems in various aspects of clinical medicine. Not the least of these have been advances in anaesthetic techniques, equipment, and available agents which now make possible the contemplation and execution of surgery on "bad risk" patients under such deliberately altered conditions of body economy as hypothermia and extracorporeal circulation. Under such conditions the possibility then arises that the side-effects of a compound or group of compounds may have much more significance than previously.

The introduction of curare into clinical anaesthesia in 1942 by Griffith and Johnson[1] has led to a steadily increasing use of muscle relaxants. A voluminous literature has developed relating to their mode of action both clinically and in the laboratory, and a review of these agents in man has been recently prepared by Foldes.[2]

It is well accepted that some patients exhibit an abnormal response to relaxant administration, the most vexing and probably the most familiar being that of prolonged hypoventilation or apnoea. Having excluded such causes of respiratory failure as hyperventilation with suppression of the Hering-Breuer reflex, hypocarbia secondary to hyperventilation, gross hypoventilation with carbon dioxide narcosis, respiratory depression secondary to hypnotics, depleted plasma pseudocholinesterase, electrolyte imbalance, and obvious overdosage of relaxant with prolonged myoneural block, there remains a group in which no ready cause is apparent and where a direct central effect of relaxants might be considered.

The purpose of the present study was to assess the central activity of five muscle relaxants in healthy dogs under conditions which excluded all of the abovementioned factors.

METHOD

The investigation of the central action of drugs makes it necessary to separate the central from peripheral effects of the injected agent. To accomplish this, the classical isolated-head technique described by Heymans and Ladon[3] and Heymans and Heymans[4] was used. The method utilizes the cardiovascular system of one

*A preliminary report of this work was presented at the 1960 Fall Meeting of the American Society for Pharmacology and Experimental Therapeutics (Hersey, L. W., The Pharmacologist *2*: 86 [1960]).

†Awarded British Oxygen Canada Prize 1961.

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dog (Donor) to perfuse the head of another (Recipient) which has been separated from its body except for its nervous connections (Fig. 1).

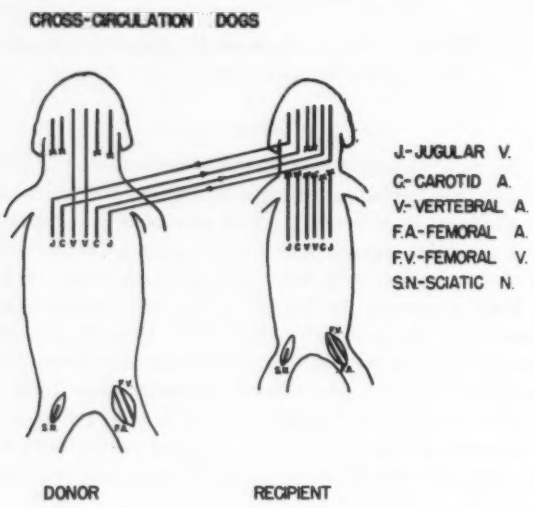

FIGURE 1

Healthy dogs of average weights of 15–20 kg. were anaesthetized with intravenous pentobarbital sodium 30 mg./kg. and one femoral artery and vein were cannulated in each dog. The arterial blood pressure of each could then be continuously recorded on a kymograph. Tracheostomy was performed on each animal and a glass T-cannula was inserted into the donor, while in the recipient a special copper tracheal cannula for attachment of a Hall pneumotachygraph was inserted. The carotid arteries and external jugular veins were isolated in both dogs and, after the donor had received 5 mg./kg. Heparin intravenously, vascular anastomoses were established (as shown in Fig. 1) between the two dogs by means of siliconized plastic catheters fitted with capped side tubes for injections. Harvard Model 607 respirators were used when the respiratory rate and/or tidal volume decreased by an arbitrary 50 per cent of control values in either animal. Rectal temperature in each animal was recorded periodically with standard mercury thermometers. The electrocardiograph and electroencephalograph of each animal were recorded on a Grass Model 5 polygraph by means of four-limb subcutaneous plate electrodes and occipital and parietal needle electrodes respectively. The respiratory activity of the recipient, measured by the pneumotachygraph, was also recorded on the Grass polygraph. Then, one sciatic nerve in each animal was isolated and divided for subsequent electrical stimulation with bi-polar electrodes and a Grass square-wave stimulator.

The adequacy of circulatory isolation from the recipient body was checked before injection of the relaxant drugs by intravenous administration of 20–40 μgm. adrenaline into the femoral vein of the donor dog. A prompt pressor response

in the donor and a reflex bradycardia and hypotension in the recipient was indicative of successful isolation.[6] A similar injection after the series of relaxant injections was done in most cases to demonstrate the persistence of circulatory isolation during the experiment.

The relaxant drug was injected into one carotid-artery cross-over tube so that it went directly into the cerebral circulation of the recipient dog. The dose of relaxant was doubled at intervals of five minutes and continuous recordings of the arterial blood pressure, EEG, EKG, and respiratory activity were made. Interrupted shocks of 40 volts and 5-msec. duration were applied to the distal end of the sectioned sciatic nerve before and two minutes after each injection of relaxant to ascertain the presence or absence of myoneural block; this response was observed visually. A total of approximately ten times the myoneural blocking dose in the donor was given and effects on the abovementioned parameters were noted in the recipient. In three experiments arterial and venous blood samples were obtained from the cross-over tubing for oxygen determinations by the Roughton-Scholander method.[5]

The following relaxants were used, one agent being used in each experiment: succinylcholine chloride (Anectine®, Burroughs Wellcome); d-tubocurare chloride (Tubarine®, B.W.); decamethonium (Syncurine®, B.W.); gallamine tri-ethiodide (Flaxedil®, Poulenc); 1,6-hexamethylene-bis-carbaminoylcholine (Imbretil®, B.W.)

Results

The present experiments revealed that, collectively, as indicated in Table I, electrocardiograph activity was unimpaired in the absence of hypoxia. Arterial blood pressure in both donor and recipient was well maintained in every experiment at all the dosage levels employed, except for the d-tubocurare group. In the d-tubocurare group, a significant hypotension was observed in each experiment and intravenous methoxamine or metamphetamine was given via the donor femoral vein to maintain perfusing pressures.

Two principal positive findings resulted from these experiments. First, in the experiments with decamethonium, curare, and hexamethylene bis-carbaminoylcholine (HMCC), signs of cerebral stimulation were elicited. With decamethonium both EEG and clinical evidence of convulsions following intra-arterial doses of 0.32 and 0.64 mg./kg. were noted (Fig. 2) in two of the three experiments with this agent. In one experiment with curare, although no clinical evidence of convulsions was observed, there was questionable EEG evidence of cerebral stimulation. Finally, in one of the four HMCC experiments there was EEG and clinical evidence of convulsive activity. In all of these experiments oxygenation and cerebral perfusion was felt to be adequate and in the HMCC experiment the arterial oxygen content at the time of convulsions was 17.6 volumes per cent. This finding excluded the possibility that hypoxia was the cause of deranged cerebral activity.

Secondly, respiratory depression was significant and marked in all experiments. This depression was shown to be independent of myoneural block. In each case there was respiratory depression of over 50 per cent in the recipient in the presence

TABLE I

SUMMARY OF EFFECTS OF RELAXANTS

		Doses required for (mg./kg.)				Coincident effects on				
		myoneural junction block		tidal volume reduced 50 per cent		art. press (mm. Hg)				
		donor	recip.	donor	recip.	donor	recip.	EEG	EKG	Notes
Succinylcholine	1	0.4	*	0.4	0.2	90	100	level 1–2	unchanged	corneal reflex present. #1
	2	0.4	*	0.4	0.2	90	110	level 1–2	uncbanged	not on artif. vent.
	3	0.4	*	0.4	0.2	100	130	level 1–2	unchanged	Hypoxic EKG and EEG
	5	0.8	*	0.8	0.2	80	100	level 1–2	unchanged	changes after 0.8 mg./kg.
C10	6	0.16	*	0.16	0.16	120	120	level 1–2	unchanged	corneal reflex present. EEG
	7	0.32	*	not reduced 50%		120	120	0.32 mg./kg.-EEG convulsive activity	S-T seg.after 0.64 mg./kg.	convulsive activity in 7 and 8 after 0.32 mg./kg.
	8	>0.64	*	>0.64	0.16	90	110	0.32 mg./kg. EEG convulsive activity	unchanged	
Curarine	9	0.8	*	0.8	1.6	70	80	? convulsion after 1.6 mg./kg.	unchanged	corneal reflex present
	10	0.4	*	0.4	0.2	60	80	level 2	unchanged	vasopressor support in all
	11	0.4	*	0.4	0.4	70	70	level 2	unchanged	experiments
Gallamine	12	1.6	*	1.6	1.6	90	110	level 2	unchanged	corneal reflex present
HMCC†	13	*	0.32 (weak)	*	0.32	110	130	level 1–2 with 13, 15, 16	unchanged	corneal reflex present
	14	0.32	0.32	0.32	0.04	110	120	convulsive activity	unchanged	
	15	0.32	0.16	0.32	0.08	100	120	post 0.02, 0.04, 0.08 mg./kg. in 14	unchanged unchanged	
	16	0.32	0.16	0.32	0.04	110	120		unchanged	

*Not blocked

†1,6-Hexamethylene-bis-carbaminoylcholine

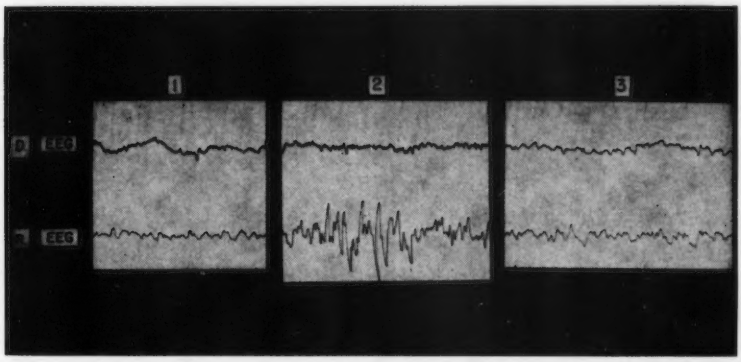

FIGURE 2. Decamethonium—convulsions. Panel 1, pre-convulsions; Panel 2, convulsive activity in R. post 0.32 mg./kg. intracarotid injection; Panel 3, 30-sec. post-convulsion, noting some flattening and increased slow wave activity, 10 mm./sec. (D, donor; R, recipient).

of an intact myoneural junction. These effects, and the doses required to produce them, are summarized in Table II. A typical tracing of respiratory depression is shown in Fig. 3.

TABLE II

RELATING MYONEURAL BLOCK TO RESPIRATORY DEPRESSION OF GREATER THAN 50 PER CENT

	mg./kg. intra-arterial to recipient							
	0.04	0.08	0.1	0.2	0.3	0.4	0.6	1.2 and over
Curarine (10)								
Myoneural junction								
donor			+	+	+	○	○	○
recipient			+	+	+	+	+	+
Respiration								
recipient		+	+	○	○	○	○	○
Succinylcholine (3)								
Myoneural junction								
donor			+	+	+	○	○	○
recipient			+	+	+	+	+	+
Respiration								
recipient			+	○	○	○	○	○
Decamethonium (8)								
Myoneural junction								
donor			+	+	+	+	○	○
recipient			+	+	+	+	+	+
Respiration								
recipient			○	○	○	○	○	○
Gallamine (12)								
Myoneural junction								
donor				+	+	+	+	○
recipient				+	+	+	+	+
Respiration								
recipient				+	+	+	+	○

+, not blocked; ○, blocked.

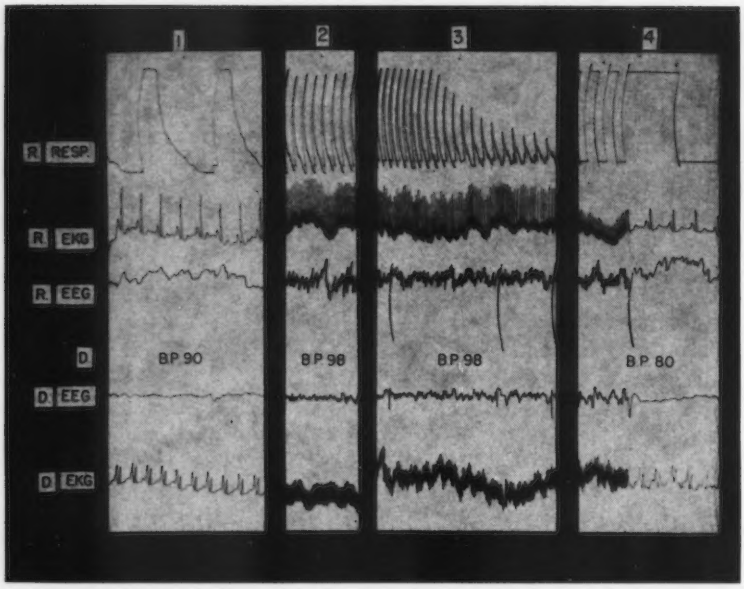

FIGURE 3. Decamethonium. Panel 1, pre-injection, 25 mm./sec.; Panel 2, pre-injection 10 mm./sec.; Panel 3, post 0.16 mg./kg. intracarotid injection, showing decline in R. respiration; Panel 4, post 0.64 mg./kg. intracarotid injection at 10 mm./sec. and 25 mm./sec., showing lack of EKG and EEG effects (D, donor; R, recipient).

The four experiments with the new agent, 1,6-Hexamethylene-bis-carbaminoylcholine (HMCC), deserve special mention in respect to both central effects on respiration and myoneural block. There was a constant and very marked decrease in both tidal volume and respiratory rate following 0.04 mg./kg. in three experiments, and following 0.32 mg./kg. in the fourth (Table I). There was no evidence of myoneural block in the donor dog until after 0.32 mg./kg. in three experiments and a block was never obtained in the donor in the fourth. In each of the HMCC experiments, however, evidence of myoneural block was demonstrated in the recipient dog with the dosages shown in Table I. This did not occur in any experiments with any of the other agents although they were conducted under the same conditions. Table III, which relates myoneural block to respiratory depression in a typical HMCC experiment, can be compared with Table II in which this same relationship is expressed with the four commonly-used relaxants. To investigate further the myoneural blocking effect of HMCC, the classic experiment of Claude Bernard utilizing the frog sciatic nerve-gastrocnemius preparation was performed on four different frogs, using control frogs with d-tubocurare. Doses of 0.025, 0.12, and 0.14 mg./gm. HMCC were injected into the dorsal lymph sac but no myoneural block was ever obtained. The control frogs received 0.15 and 0.32 mg./gm. d-tubocurare which elicited a myoneural

TABLE III

RELATING MYONEURAL BLOCK TO RESPIRATORY DEPRESSION WITH HMCC* (16)

	mg./kg. intra-arterial to recipient									
	0.01	0.02	0.04	0.08	0.1	0.2	0.3	0.4	0.6	1.2
Myoneural junction										
donor	+	+	+	+	+	+	O	O	O	
recipient	+	+	+	+	O	O	O	O	O	
Respiration										
recipient	+	+	O	O	O	O	O	O	O	

*1,6-hexamethylene-bis-carbaminoylcholine
+, not blocked; O, blocked

block in the leg with intact blood supply, as might be expected. On the other hand, in dogs the Claude Bernard experiment revealed that in the leg with occluded blood supply no block occurred, whereas in the limb with intact circulation a block occurred. This block occurred at the myoneural junction because it was shown that direct stimulation of the muscle elicited a response, and stimulation of the central end of the cut sciatic nerve produced a pressor response showing that the nerve could still conduct impulses. Later studies demonstrated that intrathecal injections of Imbretil were capable of producing myoneural block in the perfused leg, but again occlusion prevented its action in the other leg. Further experimental work is in progress to elucidate this block.

DISCUSSION

The present study indicates that with each of the agents a very definite respiratory depressant effect can be elicited which is independent of peripheral moyneural block. The findings of Harmel *et al.*[7] in cross-circulation experiments also showed a central respiratory depression. Cardiovascular effects were minimal except with d-tubocurare which consistently caused hypotension with larger doses.

Previous work on the central effects of relaxants following the introduction of curare into clinical anaesthesia in 1942 has been largely inconclusive. McIntyre *et al.*[8] and Ellis *et al.*[9] in experiments with cats and dogs noted central depression following intravenous curare as evidenced by the EEG and by respiratory arrest. Anoxic phenomena were not ruled out, and Everett,[10] in experiments on cats, rabbits, and rats, felt that d-tubocurare had little central effect *per se*, but that if anoxia developed, then convulsions occurred. Salama and Wright[11] demonstrated that direct application of curare to the exposed cortex or via subarachnoid injection resulted in stimulation of vasomotor, respiratory, cardiac, and other autonomic centres, but again the adequacy of cerebral oxygenation was not clarified. McIntyre *et al.*[12] concluded that the conflicting results were due in part to dosage and mode of application. The evidence to that time suggested that d-tubocurare was capable of modifying central nervous system activity independent of secondary anoxic effects.[11,13,14] It does not follow that non-curarizing dosages are devoid of all central action and the present experiments with d-tubocurare indicate a definite central effect: respiratory depression or apnoea was

produced repeatedly in the presence of an intact myoneural junction in the recipient animal.

Haber *et al.*[15] in their investigation of the site of the inspiratory and expiratory centres in the medulla using microelectrodes found no evidence of central depression of respiratory discharges following succinylcholine up to fifty times the paralyzing dose, or with d-tubocurare and decamethonium. Similarly, Paton and Zaimis[16] found no change in phrenic-nerve action potentials following d-tubocurare and decamethonium in paralyzing doses until asphyxia supervened, at which time discharges were intensified. These findings are at variance with the results of our study and with those of Harmel *et al.*[7]

In the present experiments it appears that the muscle relaxant agents are indeed able to depress respiratory activity when injected directly into the cerebral circulation. This has been shown with each experiment, when respiratory activity was depressed significantly in the presence of an intact myoneural junction. We believe, also, that these experiments indicate that decamethonium in particular and, to a lesser extent, curare and HMCC are able to evoke cerebral stimulation when injected under the previously described conditions.

The manner in which the agent in question reaches its target—in this case the central nervous system—inevitably evokes the blood-brain or blood-tissue barrier. By intra-arterial injections the cerebral circulation could be selectively perfused with the agent unaltered by metabolic processes.

In view of the apparent central effects discussed, the factors which are thought to influence blood-brain or blood-tissue permeability must be briefly considered. Paton[17] says the literature relevant to clinical work is unsatisfactory. Several workers—Paton,[17] Foster,[18] and Hunter[19]—cite electrolyte derangements, particularly decreased potassium ion concentration, as contributing to increased permeability of the blood-brain barrier and consequent abnormal effects following administration of relaxants.

Cole[20] and Comroe and Dripps[21] mention histamine release which is manifested in man by skin flushing (vasodilatation), hypotension, and bronchospasm, and in dogs by gastrointestinal haemorrhages. It is interesting to speculate whether widespread changes in tissue permeability, including the blood-brain barrier, may follow vascular injections of relaxants—all of which have been shown to exhibit histamine-releasing activity[22]—although in one study Paton and Zaimis[16] found no evidence of histamine release following curare injection. Payne[23] cites cases of transient gallamine-induced hypotension of 20–100 mm. mercury following non-myoneural blocking doses and, noting that the hypotension was relieved by atropine, concluded that the mechanism was not central. Biological variation and the stimuli required to provoke histamine release from the perivascular or skin mast cells[24] are obviously significant.

Besides the mechanisms of electrolyte imbalance and histamine as they affect tissue permeability in general and the blood-brain barrier in particular, there are two other factors which have been considered. The first is the effect of elevated carbon dioxide levels which was found in a study by Payne[25] to oppose the action of succinylcholine, decamethonium, and gallamine, and to enhance the action of d-tubocurare. Concomitant studies of plasma potassium ion concentration and

blood pH showed no direct relationship between plasma potassium and relaxant action. Payne suggests that changes in the degree of ionization and protein binding are responsible for changes in the permeability of the blood-brain barrier rather than hypercarbia *per se*. It is to be noted that in the present study hypoventilation and hypercarbia were avoided. The second factor is that of muscle temperature as it affects muscle relaxant activity. Bigland *et al.*[26] reported that decreased muscle temperature increased the magnitude of the effect of depolarizing agents and prolonged their action, whereas cooling reduced the magnitude and duration of non-depolarization block. The effects of total body cooling have quite recently become of much greater clinical significance with the increased scope and extent of cardiovascular and neurosurgery and with wider use of the extracorporeal circulation.

Another variable in studies of this kind is that of species resistance; the classical experiment by Smith *et al.*[27] is an example. The author himself was the experimental subject and received up to two and one-half times the paralyzing dose of d-tubocurare with no demonstrable central effects.

The new agent, Imbretil, was found to exhibit some interesting features in the experimental animal not found with the other agents. The observation that a peripheral block occurred in the limbs of the recipient despite the demonstration of circulatory isolation between the donor and the recipient's body was puzzling. Possibly there is a very marked permeability of the blood-brain barrier induced by hexamethylene carbaminoylcholine (HMCC)—to such an extent that in the recipient a significant amount reaches the isolated body via drainage from the spinal veins and causes a myoneural block without causing a similar block in the donor. The classical Claude Bernard experiment on dogs discussed earlier demonstrates the effect to be at the myoneural junction; it was also found that blockade could be induced by intrathecal injection of the Imbretil without any being administered directly into the circulation. There have been a number of clinical reports on the use of HMCC (Imbretil), the consensus being that a "dual block" was involved—with an initial depolarizing type being followed by a longer-acting non-depolarizing block which could be antagonized by neostigmine.[28,29,30] Reis[31] observed that ganglionic blocking agents tended to potentiate the myoneural block. Dripps[32] remarked on the variable and unpredictable duration of respiratory depression and the lack of a reliable antagonist to this depression. These clinical studies on the unpredictability of blockade together with the excellent abdominal relaxation "almost equivalent to that obtained with spinal anaesthesia"[32] taken with the results of the present study would tend to support the concept of a high degree of permeability of the central nervous system to this agent and a not insignificant central effect *per se*. Certainly, further work is indicated in this field and further experimental investigation is contemplated.

Summary

Fifteen experiments utilizing cross-circulated healthy dogs were performed to investigate the purely central action of succinylcholine chloride, decamethonium, d-tubocurarine chloride, gallamine tri-ethiodide, and 1,6-hexamethylene-bis-carbaminoylcholine bromide.

The experiments were conducted under conditions of normothermia and controlled oxygenation and perfusion pressure to reduce the variables influencing the central nervous system.

All the relaxant drugs used were considered to exhibit central activity, apart from their well-known activity at the myoneural junction. Hexamethylene carbaminoylcholine, in particular, appeared to exert a marked central action because of its ability to permeate the blood-brain barrier with relative ease.

By far the most significant central effect was on the respiratory centre, causing depression and apnoea in the isolated recipient body. The dosage required to produce central respiratory arrest or depression was found to approximate closely that required to produce a peripheral myoneural block in the donor body.

Significant tachyphylaxis was observed only with decamethonium, where it was difficult to effect myoneural block and long-lasting central respiratory depression.

Vasomotor effects were not noted except with d-tubocurare: increasing doses resulted in increasing hypotension.

Cerebral stimulation was elicited in two of the three decamethonium experiments, one of three curare experiments, and one of four hexamethylene carbaminoylcholine experiments.

No cardiac effects attributable to these agents were noted. A hypothesis for the possible action of hexamethylene carbaminoylcholine is suggested in the light of the results obtained in these experiments and from other published clinical reports. Further work in this field is indicated.

The increasing significance of altered body economy and the increased scope and extent of surgery in the presence of such conditions suggest to us that the side-effects of muscle relaxants may come to assume a more significant role than previously.

Species variation in the effects of myoneural blocking agents undoubtedly occurs, but it is felt that the present study, combined with the clinical appraisals, leads to the belief that central activity can indeed be significant in certain cases.

The nebulous blood-brain barrier offers a wide field for further investigation of drug action.

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Résumé

Nous avons fait quinze expériences en employant des chiens en bonne santé en circulation croisée, pour étudier exclusivement l'action centrale du chlorure du succinylcholine, du décaméthonium, du chlorure de d-tubocurarine, du tri-

iodure de gallamine et du bromure 1, 6-hexaméthylène-biscarbaminoyl-cholines.

Ces expériences ont été faites en maintenant la température normale mais en contrôlant l'oxygénation et la pression de perfusion dans le but de diminuer le nombre de facteurs susceptibles d'influencer le système nerveux central.

Tous les médicaments myorésolutifs nous ont semblé produire une activité centrale en plus de leur action bien connue à la jonction myoneurale. L'hexaméthylène carbominoylcholine en particulier a semblé produire une action centrale marquée à cause de sa facilité à traverser la barrière sang-cerveau.

L'action, de beaucoup la plus marquée sur le système nerveux central, s'est manifestée sur le centre respiratoire en provoquant une dépression et une apnée sur le récepteur isolé. La dose nécessaire pour provoquer un arrêt respiratoire central ou une dépression semble être voisine de la dose requise pour produire un blocage myoneural périphérique chez le donneur.

Une tachyphylaxie importante a été observée seulement avec le décaméthonium avec lequel il a été difficile de produire un blocage myoneural et une dépression respiratoire centrale d'une certaine durée.

Nous n'avons pas observé d'effets vaso-moteurs si ce n'est avec le d-tubo dont des doses croissantes ont provoqué une hypotension proportionnelle.

Une stimulation cérébrale a été manifeste au cours de deux des trois expériences avec le décaméthonium au cours d'une des trois expériences avec le curare, et au cours d'une des quatre expériences avec l'hexaméthylène carbominoylcholine.

Nous n'avons observé aucun effet de ces médicaments sur le cœur. A la suite des travaux publiés sur ce sujet et des renseignements recueillis au cours de ces expériences, nous émettons l'hypothèse d'une action possible sur le cœur de l'hexaméthylène carbominoylcholine. Il s'impose de continuer la recherche dans ce domaine.

L'importance croissante que prennent les perturbations organiques et l'extension progressive de la chirurgie dans ces circonstances nous portent à croire que les effets secondaires des myorésolutifs peuvent venir à jouer un rôle plus important qu'ils ne l'ont fait antérieurement.

Sans doute, il existe des variantes dues à l'espèce dans les effets du blocage myoneural, mais nous avons l'impression que l'étude actuelle, en plus de l'évaluation clinique, conduit à la conclusion que l'activité centrale, en certains cas, peut être assez marqueé.

Cette vague barrière sang-cerveau ouvre un champ considérable de recherches sur l'action des médicaments.

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BRONCHOPULMONARY RESISTANCE IN PREGNANCY

JAMES H. KERR, M.A., M.B.*

THIS PAPER is concerned with observations of expired bronchopulmonary resistance values in normal pregnant women, in those with evidence of pre-eclamptic toxaemia, and in pregnant asthmatics. The importance to anaesthetists of increases in bronchopulmonary resistance in pregnancy revolves around its appearance as a dominent feature in a syndrome with which nearly all have had either direct or indirect experience, the acid-aspiration syndrome, or Mendelson's asthmatic-like reaction.[1]

This syndrome was described by Mendelson in a paper 15 years ago. He differentiated between the pulmonary sequelae of the aspiration of solid vomitus and those of the aspiration of liquid vomitus during general anaesthesia for obstetrics. These latter he referred to as the asthmatic-like reaction. Since then this syndrome has generally become known as Mendelson's syndrome. These cases, in some of whom the actual inhalation of vomit was not noticed, developed cyanosis, tachycardia, and dyspnoea; the chest showed rales and rhonchi over the affected areas of the lungs and radiography revealed no evidence of pulmonary lobar collapse but of diffusely scattered opacities. The author advised that treatment should be directed to the relief of the bronchiolar spasm and the ensuing cardiac embarrassment. In a further paper,[2] Parker described the autopsy findings in four such cases of pulmonary death following obstetric anaesthesia. In these there was no evidence of airway obstruction, only small quantities of aspirate being found in the bronchial tree. The history of these cases revealed that the vomiting had occurred prior to or during anaesthesia, but that the onset of the fatal symptoms might come later, the patient being in an apparently satisfactory condition in the interval. It was as a consequence of personal experience of two such cases, one fatal, that a search of the literature was made in an attempt to uncover any unusual situation in pregnancy which might lead to these pulmonary sequelae in apparently fit young women.

That a unique disturbance exists in pregnancy which might facilitate the appearance of the reaction is suggested by the work of Kapeller-Adler.[3] She has shown that strong histaminase activity is found in the blood of pregnant women, whereas no such activity is detectable in that of the non-pregnant. The source of the enzyme has been shown by Swanberg[4] and others to be the placenta. Kapeller-Adler's figures show that in normal pregnancy there is little alteration in the histamine content of the blood cells and plasma accompanying the increased histaminase content of the serum. In the toxaemias, however, as the severity of

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the condition increases, histaminase activity falls and there is an apparent shift of histamine from the cells to the plasma (Fig. 1). This she attributes to the

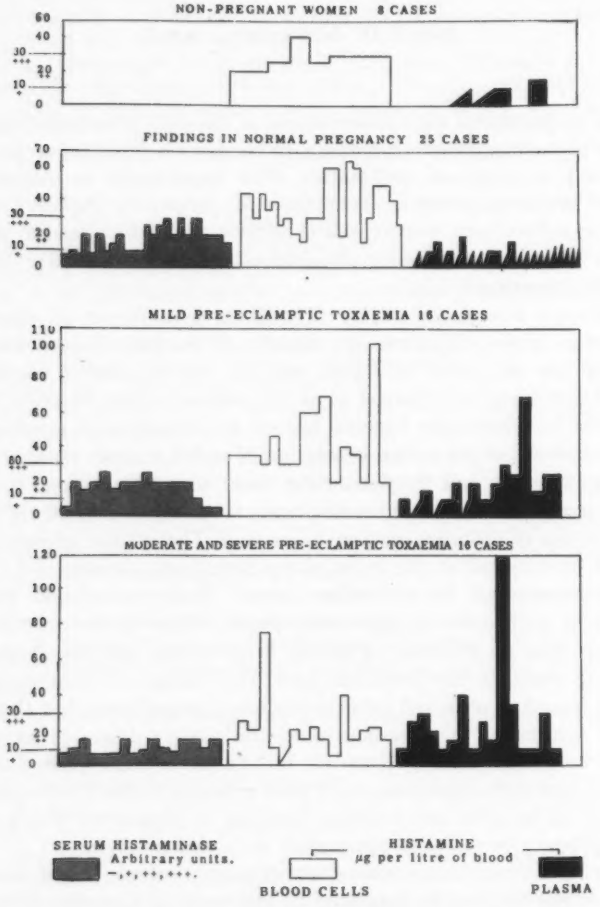

FIGURE 1. Histamine and histaminase levels in normal pregnancy and pre-eclampsia. This histogram is composed from the figures given by Kapeller-Adler. The abscissae represent the number of women concerned, the columns in each item correspond in order to the same patient. (By kind permission of Dr. Kapeller-Adler and the editor of the Lancet.)

increased facility of the histamine to move from within the cell to the tissue fluids. In the advanced toxaemias, situations may arise in which the plasma histamine level may exceed that of the cells. She concludes that the histaminase

might serve as a protective measure against histamine intoxication and that the amount circulating is proportional to the amount of living placental tissue.[5] This being so, a fall in the serum histaminase level following the removal of its source, with a concurrent slow fall in the plasma histamine, might lead to a critical level, with pulmonary symptoms, being attained after an interval.

In order to investigate the hypothesis[6] that this elevated plasma histamine level might be indicted as the cause of the bronchospasm in Mendelson's syndrome, a project was set up to make measurements of bronchopulmonary resistance in pregnancy. It also seemed possible that the elevated histamine in the plasma in the pre-eclamptic toxaemias might cause changes in the bronchopulmonary resistance in the course of pregnancy. For this reason, both normal and pre-eclamptic patients would be studied, and in both groups the effects of the administration of an antihistamine on the lungs would be investigated. Tripelennamine was selected for the purpose as it possesses slight central depressive effects and minimal adrenaline reversal activity.

The method of measuring the bronchopulmonary resistance was that of Clements,[7] utilizing a repetitive interrupter technique. This technique analyses solely expiration, and the results are expressed as cm. H_2O/L./sec., at 1 L./sec. This is necessitated by the exponential character of human airway resistance, the value, determined by Ainsworth, being 1.6.[8] The interrupter used in this investigation had a coefficient of resistance of 3.94 cm. H_2O/L./sec. and an exponent of 1.54. Patients were observed at intervals from about the seventh month of their pregnancy until term, additional records being taken when possible during labour and following delivery. The great majority of the post-delivery measurements were made in the first few hours. Unfortunately, a few were not obtained until some 24–48 hours had elapsed. All women were carefully screened for evidence of pulmonary and cardiac conditions which might influence the results.

The first group was of eighteen normal pregnant women who showed no evidence of pre-eclamptic toxaemia at any time during the period of observation. They received no drugs other than vitamins during their pregnancy. Sedation during labour excluded all phenothiazine derivatives and antihistamines. The values obtained for each patient were tabulated according to the week of the pregnancy in which the record was made. In order to do this, it was assumed that parturition took place at the fortieth week. From these tables the average results obtained from the records on each particular week were calculated and reduced to the nearest half centimeter of water. The maximum value obtained from this group of patients at any time was 3.5 cm. H_2O/L./sec. and the minimum 1.5 cm. H_2O/L./sec. The averages obtained at each of the weeks fell between 3 and 2 cm. H_2O/L./sec.

The second group of 11 women, with normal pregnancies, were given tripelennamine 50 mg. t.i.d. during the latter month of their pregnancies. Only one of these patients reported drowsiness and her dosage was reduced to 50 mg. b.i.d. Two of these patients were given intramuscular doses of tripelennamine 25 mg. during labour. The recordings were made on the same schedule as the first group and calculated in the same manner. The maximum reading obtained was 3.5 cm.

H_2O/L./sec. and the minimum 2.0 cm. H_2O/L./sec. The averages obtained at each week was 3 cm. H_2O/L./sec. during pregnancy and labour, falling to 2.5 cm. H_2O/L./sec. after parturition.

Five of the women from these first and second groups were seen again six weeks following delivery and their non-pregnant bronchopulmonary resistance averaged 2.5 cm. H_2O/L./sec. with a maximum and minimum respectively of 3.0 and 2.0 cm. H_2O/L./sec. (Fig. 2).

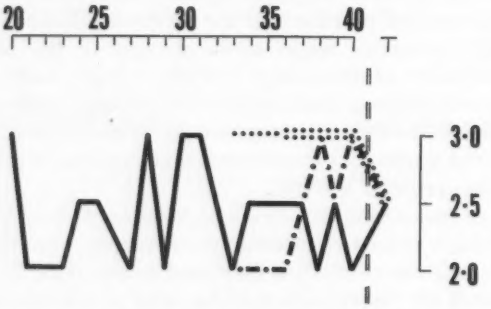

FIGURE 2. Bronchopulmonary resistance in pregnancy. Abscissa, week of pregnancy; ordinate, cm. H_2O/L./sec.; —— values obtained in normal pregnant women; .... values obtained in normal pregnant women and : : : : during the period of oral administration of tripelennamine; -·-· values obtained in women with evidence of pre-eclamptic toxaemia. The time of parturition is denoted by the interrupted vertical lines.

From these results it was concluded that expired bronchopulmonary resistance was unaffected by normal pregnancy, and was of a value of 2.0 to 3.0 cm. H_2O/L./sec. when obtained by this method. Furthermore, the administration of tripelennamine appeared to have no effect on these values.

A third group of 8 patients who showed evidence of pre-eclamptic toxaemia were then observed. The average figures, obtained in the same manner as in the previous groups, showed their bronchopulmonary resistance to be between 2.5 and 2.0 cm. H_2O/L./sec. with a maximum reading of 5.0 and a minimum of 1.5 cm. H_2O/L./sec. Two of these cases were treated with a low salt diet, two with a diuretic and a low salt diet, two by diuresis and tripelennamine, and two by tripelennamine alone. Such a variety of treatment in so small a series denies the possibility of arriving at any finite conclusion as to the relationship between bronchopulmonary resistance and toxaemia of pregnancy. These toxaemias, it must be pointed out, were all of the mildest order. The more advanced cases of toxaemia are not suitable for study in the manner here used, as the necessary sedation renders the patients unable to co-operate adequately. However, one point of interest does arise from the figures obtained; the only recordings where the bronchopulmonary resistance exceeded the value of the maximum obtained in either of the foregoing normal groups were in an untreated case, or in one in which a low salt diet alone was used. The remainder of the figures were within

the range of the normal averages. The values obtained in one patient treated by diuretics and low salt intake diet demonstrated the effect of adequate weight control. Her resistance fell progressively from 5.0 cm. H_2O/L./sec. at the twenty-sixth week of pregnancy, when treatment was instituted for excessive weight gain, to 2.0 cm. H_2O/L./sec. at term.

The observations on this group of patients do little other than suggest that toxaemia may be associated with increased bronchopulmonary resistance. This may be due to passive swelling of the lining cells of the bronchioles.[9]

The following case histories, excluded from the previous groups for reasons which will be apparent, are given to illustrate the effects of tripelennamine when used for the treatment of bronchospasm which was clinically evident.

Case 1

This 24-year-old primiparous woman was first seen at the thirty-fifth week of pregnancy. She gave a history of a facial dermatitis following both sulphonamide and penicillin therapy, and at the time had suffered an acute coryza which she stated had begun one week previously, but was resolving. Her bronchopulmonary resistance was then 3.5 cm. H_2O/L./sec., and on auscultation of the lungs expiratory rhonchi were heard. After a week taking tripelennamine mg. 50 t.i.d. the value was 3.0 cm. H_2O/L./sec. and the chest was clear of rhonchi. At the thirty-seventh week, still taking tripelennamine, the value was again 3.5 but the chest remained clear; this rise coincided with the first appearance of albuminuria and hypertension. Early in her labour which began two weeks later, the resistance rose to 5.0 cm. H_2O/L./sec. and her chest once again contained rhonchi; an intravenous dose of tripelennamine was given at the time and immediately following this the rhonchi disappeared and the resistance fell to 4.0 cm. H_2O/L./sec. Her post-partum record gave a value of 3.5 cm. H_2O/L./sec.

Case 2

This patient, who was first seen at the thirty-third week of pregnancy, had had five previous pregnancies which all miscarried. She was aged 34 years and gave no history of pulmonary or cardiac conditions, nor of asthma or other sensitivity. She complained that as this pregnancy had proceeded she had become wheezy and was coughing, especially at night. Her bronchopulmonary resistance was 6.0 cm. H_2O/L./sec. She was given Promethazine mg. 10 q.i.d. for a week and this value fell to 3.0 cm. H_2O/L./sec. She was advised to continue taking the promethazine, but this she failed to do and on her next weekly visit she was extremely wheezy and was given promethazine mg. 20 orally at that time. Later the same day she appeared at the hospital with gross dyspnoea and cyanosis; coarse rhonchi were heard in her lung fields. The resistance had reached 15.5 cm. H_2O/L./sec. Ten mg. promethazine were given intravenously and a quarter of an hour later a resistance of 7.5 cm. H_2O/L./sec. was recorded. In a further fifteen minutes, she was breathing freely and left the hospital. Unfortunately, no further recordings were made, but she continued to take promethazine for the rest of her pregnancy which she carried uneventfully to term. It is to be noted that dependent oedema was found at all of this patient's prenatal clinic visits.

Case 3

This 26-year-old multiparous woman had had asthma for years; in each of three previous pregnancies which she carried to term, the asthma had become much worse. When first seen, she had been in hospital for four days in status asthmaticus and had proven refractory to aminophylline and cortisone therapy; she was in her thirty-ninth week of pregnancy, orthopnoeic, exhausted, and unable to sleep. In addition, she had produced a melaena and was anaemic. At this time, her bronchopulmonary resistance was about 19.0 cm. H_2O/L./sec. (repeated records were not feasible in this case). Intravenous tripelennamine mg. 25 was given; subjective relief was immediately obtained, but clinically there was no evidence of resolution of the bronchospasm. The resistance, 20 min. after the injection, had fallen to 11 cm. H_2O/L./sec. Intramuscular tripelennamine was maintained until after her delivery, but occasional intravenous booster doses had to be given. Three weeks after her delivery, her bronchopulmonary resistance was 10.0 cm. H_2O/L./sec. and at this time she stated that she was as well as at any time in recent years.

Case 4

In this case, it was not possible to obtain any measurements, initially because of the patient's critical condition, and later on account of a language barrier and lack of co-operation. The woman was in labour in her fifth pregnancy, in the later stages of which her uterine contractions had become violent; she suddenly collapsed, her pains ceased, and the foetal heart was no longer heard. A diagnosis of a ruptured uterus was made and an immediate laparotomy performed. During induction of anaesthesia, she regurgitated stomach contents which were sucked out under direct laryngoscopy; the hypopharynx was cleared and the vocal cords were noted to be in spasm; these relaxed with administration of a depolarizing agent. No vomitus was seen in the upper trachea, and a cuffed endotracheal tube was inserted. Anaesthesia was maintained on cyclopropane and oxygen with succinyl-dicholine relaxation and intermittent positive pressure respiration. At the end of the procedure, her blood pressure was satisfactory, her colour good, her chest clear on auscultation, and she was conscious within a few minutes. The blood loss had been heavy and she had received a 1,500 ml. transfusion. On transfer to the recovery room, a further 500 ml. of blood containing hydrocortisone mg. 100 was set up. One hour later she became cyanosed and her breathing became laboured; examination of the chest revealed widely scattered rhonchi and rales. Aminophylline gm. 0.35 was given intravenously but little effect was noted. Forty-five minutes after this, her blood pressure had fallen to 90/50 and her cyanosis and laboured respirations were unchanged despite oxygen therapy. At this time, tripelennamine mg. 25 was given intravenously; there was an immediate and complete release of the bronchospasm; on auscultation of the lungs, only rales could be detected. Approximately twelve hours later, there was some return of the rhonchi but these resolved with a further intravenous dose of tripelennamine. From this time onwards, she was maintained on intramuscular injections of the drug until she was able to take oral doses. In addition, she was digitalized, given antibiotics, diurectics, and continued cortisone therapy. After

two days, when she showed evidence of a pulmonary lobar collapse, she coughed well and produced some bloodstained sputum. From then on she improved more rapidly and eventually left the hospital with a clinically and radiologically clear chest. Sputum specimens were examined without success for evidence of amniotic fluid embolus, and electrocardiograms showed no evidence of coronary occlusion; changes due to anoxia and some right ventricular strain were noted, however. This case was considered a classic example of Mendelson's syndrome and the dramatic resolution of the bronchospasm by the administration of tripelennamine was noted.

Discussion

The values for bronchopulmonary resistance in normal pregnancy have been recorded, using a direct measurement technique. That the administration of an antihistamine to normal pregnant women does not alter these values has been demonstrated.

A small group of women with evidence of pre-eclamptic toxaemia was investigated; a variety of treatments to these patients precluded an assessment of the effects of the pre-eclampsia upon the bronchopulmonary resistance, but it was noted that higher values occurred in this group.

Four selected cases in which antihistamines were used successfully for the treatment of bronchospasm occurring in association with pregnancy are also presented. One of these cases was a known asthmatic. The use of antihistamines in the treatment of asthma aggravated in pregnancy must be considered both in the light of the abnormal plasma histamine levels and Dale's[10] theory of cellular response to histamine. Dale postulates that cells may respond to intrinsically as well as extrinsically released histamine, the latter being carried from distant cells to the effector cells in the body fluids. In asthma the bronchial muscle responds to intrinsically released histamine which accounts for the lack of response to antihistamines.[11] In pregnancy these cells are exposed to additional histamine borne by the plasma, and it would seem that the exposure of these same cells to a specific antihistamine via the same route would result in rendering the cellular surface unsusceptible to any histamine reaching it. This is also the basis for advocating the use of antihistamines to protect the lungs of pregnant women, with or without evidence of pre-eclampsia, from the raised plasma histamine levels and the part played by antihistamines in its control. It is, however, considered to be of greater importance to the toxic patient. Examination of the autopsy reports[12] of seven maternal deaths attributable to anaesthesia revealed that five had pathological evidence of pre-eclamptic toxaemia; the lungs in three of these five cases were similar to those described by Parker. Two of the seven cases, without evidence of pre-eclampsia, also gave the same picture. In only one of these subjects was vomiting known to have occurred. In the one case of Mendelson's syndrome here reported the successful action of intravenous tripelennamine is shown.

The other two recorded cases demonstrated the action of antihistamines used to treat bronchospasm occurring in the course of pregnancy.

Conclusion

Measurement of bronchopulmonary resistance in mild toxaemias does not reveal deviation from the normal range. Further work is necessary, in the severer degrees of toxaemia to elucidate the effect of the condition upon bronchopulmonary resistance.

The four case reports are considered to suggest that antihistamines may be effective in the treatment of bronchospasm associated with pregnancy and obstetric anaesthesia, and use of these drugs is advocated.

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Résumé

En employant une technique de mesure directe, nous avons établi les valeurs de résistance bronchopulmonaire au cours de la grossesse normale. Nous avons démontré que l'administration d'un antihistaminique à des femmes enceintes normales ne change en rien ces valeurs.

Nous avons examiné un petit groupe de femmes manifestant des signes de toxémie pré-éclamptique. Différents traitements chez ces malades laissaient prévoir une diminution des effects de la prééclampsie sur la résistance bronchopulmonaire, mais nous avons observé des données plus élevées dans ce groupe.

Nous avons également présenté quatre cas choisis, chez qui le traitement aux antihistaminiques a été un succès pour vaincre le bronchospasme survenant au cours de la grossesse. Une de ces malades était une asthmatique connue. L'usage des antihistaminiques dans le traitement de l'asthme, aggravé par la grossesse, doit être étudié en songeant au double aspect de la présence de taux anormaux d'histamine dans le plasma et de la théorie de Dale sur la réponse cellulaire à l'histamine. Dale postule que les cellules peuvent répondre aussi bien à une libération intrinsèque qu'à une libération extrinsèque d'histamine; dans cette dernière éventualité, l'histamine peut être apportée par les liquides de l'organisme de cellules situées à distance à des cellules effectrices.

Dans l'asthme, le muscle bronchique répond à une libération intrinsèque d'histamine. C'est pourquoi on n'obtient pas de réponse à l'administration d'antihistaminique.

Au cours de la grossesse, ces cellules sont inondées par une quantité additionnelle d'histamine apportée par le plasma, et il semblerait que si ces cellules recoivent de la même façon un antihistaminique spécifique, leur surface cellulaire deviendrait insensible à toute histamine qui pourrait les atteindre. C'est en nous basant sur ces données que nous employons des antihistaminiques pour protéger les poumons des femmes enceintes, avec ou sans signes de prééclampsie, contre les taux élevés d'histamine dans le plasma, et à cause de la part jouée par les antihistaminiques sur leur contrôle.

Cependant, cela semble plus important chez les malades intoxiquées. L'analyse des rapports d'autopsie de sept morts maternelles attribuables à l'anesthésie nous apprend que cinq d'entr'elles présentaient des signes pathologiques de toxémie prééclampsique; les poumons de trois de ces cinq malades ressemblaient à ceux qu'a décrits Parker. Deux des sept malades, exemptes de signes de prééclampsie, ont présenté le même tableau. Chez une seule de ces malades, nous avons constaté des vomissements. Dans le seul cas de syndrome de Mendelson rapporté ci-contre, nous avons observé l'action bienfaisante du trépelennamine intraveineux.

Les deux autres cas rapportés illustrent l'action des antihistaminiques pour traiter le bronchospasme survenant au cours de la grossesse.

L'évaluation de la résistance bronchopulmonaire chez les cas de toxémie légère ne dévie pas beaucoup de la moyenne. Il faudra pousser la recherche davantage chez les cas de toxémie plus grave pour préciser les effets de cette pathologie sur la résistance bronchopulmonaire.

Les quatre cas rapportés nous incitent à affirmer que l'emploi des antihistaminiques peut être efficace pour le traitement du bronchospasme au cours de la grossesse et de l'anesthésie obstétricale, et nous préconisons l'usage de ces médicaments.

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SYMPATHO-ADRENAL RESPONSES DURING GENERAL ANAESTHESIA IN THE DOG AND MAN*†

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THE ROLE of the sympathetic nervous system in the maintenance of circulatory homeostasis during general anaesthesia, some aspects of which have recently been reviewed,[1] is both interesting and important, but remains to some extent enigmatic. During the past few years, with the aid of a chemical method which measures plasma adrenaline and noradrenaline with reasonable accuracy and sensitivity, we have studied the effects of haemorrhage,[2,3] adrenergic blocking agents,[4] apnoeic oxygenation,[5,6] and hypercarbia,[7] organic buffering agents,[8] and some aspects of general anaesthesia;[9,10] clinically, measurements have been made in patients with adrenal medullary tumours[11,12] and following circulatory occlusion during hypothermia.[13] This paper is concerned with the documentation of plasma catecholamine levels, and with some attempts to interpret the sympatho-adrenal activity which these represent, during general anaesthesia in the dog and man.

METHOD

Animal Experiments

In the majority of experiments, dogs (total number 56, average weight approximately 10 kg.) were lightly anaesthetized with minimal amounts of 2.5 per cent thiopental (usually less than 200 mg.), and the trachea was intubated with a no. 9 or 10 cuffed Magill tube. After injection of a few millilitres of 1 per cent lidocaine into the groin (to minimize the possibility of reflex effects from tissue trauma), a femoral artery was cannulated for removal of blood samples and recording of arterial pressure (Statham transducer Model P 23 A, Sanborn recorder). In several studies (see Results, Groups I and III), an intravenous infusion of succinylcholine (0.1–0.2 per cent) was then started, this being continued at a very slow rate during the subsequent period of inhalational anaesthesia. In all experiments, except those following adrenalectomy, Heparin, 2 mg./kg. was given intravenously. An equal volume of normal saline was injected intravascularly immediately following withdrawal of each blood sample.

The dogs in Group I were ventilated, in a semi-closed system, with an Emerson respirator modified for intermittent positive pressure ventilation (10–15 cm. H_2O) by the addition of an electrically-driven flanged wheel which "triggered" the respirator at a rate of about 15 per min. A Waters soda lime canister was

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interposed between respirator and endotracheal tube, the soda lime being changed at intervals of about 45 min. The anaesthetics were delivered to the respirator from a Heidbrink apparatus with the "expiratory" side occluded and a Boyle "trichlorethylene" bottle connected in series with the "inspiratory" side. A constant flow of 3 L. of oxygen per min. was used to vaporize halothane or chloroform which were placed in the Boyle bottle and maintained close to the 2-oz. mark. The concentrations of halothane and chloroform administered did not exceed 3 per cent. For the ether studies in Group I, the gas flow was increased to 5 L. per min. and was bubbled through the Boyle "trichlorethylene" bottle filled with ether to the 4-oz. mark. Cyclopropane was administered in concentrations of 25–50 per cent in oxygen, at flow rates totalling 2 L. per min.

Animals of Group II were anaesthetized with diethyl ether in a manner commonly employed for animal experimentation, the dogs being placed in a box into which a mixture of ether/air was blown. When surgical anaesthesia was reached the trachea was intubated and the animals then inhaled from a 5-L. bag into which high flows of ether/air were delivered; a loose expiratory valve was used to keep resistance low and to prevent accumulation of carbon dioxide.

The intact and adrenalectomized animals in Group III were ventilated by means of a Bird respirator (Marks IV and VIII), using positive pressure only, with a Ruben non-rebreathing valve. Ether/oxygen was delivered to the respirator by way of an E.M.O. ether vaporizer, which for most studies was set to deliver 8 per cent ether. In four intact dogs in this group succinylcholine alone was used for endotracheal intubation.

The dogs in Group IV were also ventilated with a Bird respirator, connected to a Heidbrink closed circuit; 25–30 per cent cyclopropane, in oxygen, was administered at total flow rates of 1,500 ml. per minute.

Clinical Studies

Fifty male patients, age range 21–64 years, were studied prior to and during a variety of surgical operations, *excluding* neurosurgery, thoracotomy, and all procedures carried out on patients not in the supine (or lithotomy) position. They were premedicated with atropine, 0.4–0.6 mg., and a brachial artery was cannulated with a Riley needle for removal of blood samples. For administration of ether anaesthesia a Boyle semi-closed anaesthetic apparatus was used, with a Fink or Ruben non-rebreathing valve. Following a brief induction period (nitrous oxide/oxygen), a flow of oxygen 10 L. or higher was bubbled through the Boyle ether bottle, the ether level being maintained as close to the 10-oz. mark as possible. Nitrous oxide/oxygen/halothane was administered from a Boyle machine fitted with a "Fluotec" vaporizer (Mark I or II): halothane/oxygen was given by closed circuit using the technique described by Marrett.[14] For cyclopropane/oxygen anaesthesia a closed circuit Boyle apparatus was usually employed, with manual assistance to respiration; in some patients a Blease pulmoflator was used (positive pressure only), in conjunction with a Waters soda lime canister. All patients were intubated, with a no. 10 Magill cuffed endotracheal tube.

Laboratory Determinations

Blood samples were withdrawn before and at various times during anaesthesia (see Results). For assay of plasma adrenaline and noradrenaline these comprised 35 ml., withdrawn into glass tubes moistened with a few drops of Heparin (Connaught Labs., 1,000 units/ml.), and centrifuged as soon as possible. The plasma was aspirated and applied to glass columns containing 500 mg. of alumina (Wöelm, non-alkaline Grade I; acid-washed in this laboratory). Adrenaline and noradrenaline in the plasma eluates were estimated fluorimetrically by the trihydroxyindole method,[15] as described previously,[4] but with the addition of 0.5 ml. of 1 per cent disodium ethylene diamine tetra-acetate to the final mixture before measurement of fluorescence. Errors of ±25 per cent are involved in the differential estimation of adrenaline and noradrenaline in single plasma samples and the values, which refer to μg. free base/litre of plasma, are uncorrected for losses in recovery up to 30 per cent.

In most experiments, 8-ml. blood samples were withdrawn anaerobically into syringes moistened with heparin and containing a drop of mercury. Whole blood pH, and the pH of separated plasma equilibrated at 38° C with known concentrations of CO_2, were measured by means of Radiometer pH meters, Model 22 or Model 4, and the Astrup apparatus.[16] From these pH determinations the "standard bicarbonate of separated plasma" and the CO_2 tension were calculated as described by Astrup.[17] In several most recent studies (dogs in Group IV; 12 patients anaesthetized with diethyl ether) microsamples of arterial blood were equilibrated with two CO_2 tensions;[18] the arterial pCO_2 and "standard bicarbonate" of whole blood (at pCO_2 40 mm. Hg) were then determined from the appropriate log pCO_2/pH lines.

In certain studies (Groups I and II), arterial oxygen saturation was determined spectrophotometrically.[19] Blood ether concentrations (Groups I, II, and III; 4 patients anaesthetized with diethyl ether) were estimated by a modification[20] of the dichromate method.[21] Whole blood glucose was measured (in adrenalectomized animals, Group III) according to Somogyi.[22]

Statistical Methods

Statistical analysis of the data was performed according to Snedecor[23] and included analysis of variance, utilizing designed orthogonal comparisons and tests of all comparisons among means; the t-test as applied to paired values, modified where necessary to Cochran's approximation to the Behrens-Fisher test; and r, the coefficient of linear correlation.

Results

Animal Experiments

Group I. Table I presents the averaged data obtained in dogs before and after ventilation for 90 minutes with oxygen and minimal amounts of diethyl ether, and from three other experimental groups anaesthetized with oxygen and halothane, cyclopropane, or chloroform. In these studies induction was with minimal thiopental and a slow intravenous infusion of succinylcholine (0.2 per cent) was given continuously.

TABLE I

AVERAGE RESULTS IN DOGS OF GROUP I VENTILATED FOR 90 MINUTES WITH DIETHYL ETHER (7 EXPERIMENTS), HALOTHANE (5 EXPERIMENTS), CYCLOPROPANE (5 EXPERIMENTS), AND CHLOROFORM (6 EXPERIMENTS)

	pH	pCO_2 (mm.Hg)	Separated plasma standard HCO_3^- (mM/L.)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	Mean arterial blood pressure (mm.Hg)
Diethyl Ether						
Control	7.39	33	19	0.21	0.28	144
+90′	7.32	35	18	0.81	0.50	124
Halothane						
Control	7.30	47	22	0.48	0.19	146
+90′	7.30	40	19	0.79	0.34	61
Cyclopropane						
Control	7.40	37	21	0.34	0.22	143
+90′	7.38	39	20	0.74	0.22	110
Chloroform						
Control	7.36	41	22	0.21	0.21	156
+90′	7.31	47	21	0.89	0.65	104

The values for arterial pH and pCO_2 show that in general respiratory acidosis was avoided, although isolated pCO_2 levels above 49 mm. Hg were measured in two experiments with chloroform and in one study each with halothane and cyclopropane. Changes in "separated plasma bicarbonate" demonstrate "metabolic" acid-base alterations, but the levels are also influenced by respiratory acidosis or alkalosis. This fact, and the likelihood that blood loss involved in sampling may induce a mild metabolic acidosis, renders the assessment of small changes in the non-respiratory component of acid-base balance difficult in this group of experiments. It is well recognized that diethyl ether causes a metabolic acidosis in dogs,[24] and this will be shown later in the present communication; the minor effect noted in the experiments tabulated in Table I is considered to be a result of light anaesthesia, the blood ether concentrations reaching an average maximum of only 100 mg./100 ml. after 90 minutes of anaesthesia.

The average level of plasma adrenaline increased during anaesthesia with each of the four agents studied, but the rises were slight or moderate only, and the highest (average) levels did not exceed 1 μg./L. Changes in plasma noradrenaline were variable, although small increases were measured during ether and chloroform anaesthesia. From average control levels of 0.49, 0.67, 0.56, and 0.42 μg./L. respectively, total plasma catecholamine concentration (that is, adrenaline plus noradrenaline) increased to 1.3, 1.1, 0.96, and 1.5 μg./L. after 90 minutes of ventilation with ether, halothane, cyclopropane, and chloroform respectively (Table I). Average mean arterial blood pressure was reduced by 14 per cent with diethyl ether, 58 per cent with halothane, 23 per cent with cyclopropane, and by 30 per cent with chloroform.

The results of the biochemical determinations performed on blood samples withdrawn after 15 and 45 minutes of anaesthesia have for the sake of brevity been excluded from Table I, but the plasma catecholamine levels measured at

these times were taken into account in a statistical analysis of variance carried out on the data, shown in Table II. Under the specific conditions employed for

TABLE II

ANALYSIS OF VARIANCE ON THE DATA OBTAINED IN DOGS VENTILATED WITH ETHER/OXYGEN, HALOTHANE, CYCLOPROPANE, AND CHLOROFORM (GROUP I)

Source of variation	Degrees of freedom	Adrenaline mean square	Noradrenaline mean square	Total amines mean square
Diethyl Ether				
Control vs. 15′, 45′, 90′	1	1.0098*	0.1475	1.9292*
Between dogs	6	0.9622†	0.1972*	1.1222*
Error	18	0.2219	0.0545	0.3660
Halothane				
Control vs. 15′, 45′, 90′	1	0.0836		0.1893
Between dogs	4	1.0355†		1.5796†
Error	12	0.1186		0.0887
Cyclopropane				
Control vs. 15′, 45′, 90′	1	0.2344		0.1972
Between dogs	4	1.1800†		1.1431†
Error	12	0.1041		0.1017
Chloroform				
Control vs. 15′, 45′, 90′	1	0.5117	0.2091	1.3750*
Between dogs	5	0.7584*	0.0899	0.7541
Error	15	0.1874	0.0926	0.2963

*$p < 0.05$
†$p < 0.01$

this group of studies, significant increases ($p < 0.05$) in total plasma catecholamine concentrations occurred only during anaesthesia with diethyl ether and chloroform; in the case of ether this was largely due to a significant rise in adrenaline ($p < 0.05$), while with chloroform both amines were involved. Changes in plasma adrenaline, noradrenaline, or total catecholamine concentration during halothane and cyclopropane anaesthesia were insignificant statistically. It should be noted that the marked variations "between dogs" in these experiments reflect a number of factors, among which are those caused by individual animal differences and those attributable to laboratory errors and variability.

Group II. The failure to detect more pronounced increases in plasma adrenaline and noradrenaline during ventilation with ether/oxygen was unexpected in view of previous work implicating diethyl ether as a sympatho-adrenal stimulant.[25] The frequent use of this agent for animal experimentation and student teaching suggested a study of its effects when administered in a manner commonly used in pharmacology laboratories. Ether/air was therefore given to a second group of seven animals for periods of 180 minutes, initially by delivering the vapour into a box containing the dog, thereafter by endotracheal insufflation. The results from these studies (in which thiopental and succinylcholine chloride were *not* used) are presented in Table III. The low average values for arterial pH and "separated plasma bicarbonate," becoming lower as anaesthesia continued, and the reduced arterial pCO_2, illustrate the profound metabolic acidosis and respiratory stimulation which accompany moderately deep ether anaesthesia in dogs.

Control levels of plasma adrenaline and noradrenaline could not be determined

TABLE III

AVERAGED RESULTS (7 EXPERIMENTS) IN DOGS BREATHING ETHER/AIR (GROUP II)

	pH	pCO_2 (mm. Hg)	Separated plasma standard HCO_3^- (mM/L.)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	Mean arterial blood pressure (mm. Hg)	Blood ether (mg./100 ml.)	Oxygen saturation (Percentage)
+ 45′	7.25	28	12.6	1.6	0.72	124	130	88
+ 75′	7.20	28	11.1	2.0	1.5	115	127	93
+135′	7.16	27	9.9	2.6	1.1	118	121	93
+180′	7.11	29	9.5	2.2	1.5	112	143	96

in these animals before induction of anaesthesia, but the subsequent concentrations during ether/air anaesthesia were obviously greatly increased over any measured in samples withdrawn from apparently normal conscious humans (see later in this communication), or from dogs very lightly anaesthetized with thiopental in numerous studies carried out in this laboratory.[2-10] During aperiod extending from 45 to 180 minutes after induction, average plasma adrenaline varied from 1.6 to 2.6 μg./L. and plasma noradrenaline from 0.72 to 1.5 μg./L., in these animals breathing ether/air.

The average plasma adrenaline and noradrenaline concentrations measured in this group of animals after 45 minutes of ether/air anaesthesia (Table III) were significantly higher ($p < 0.05$) than the adrenaline and noradrenaline levels (0.52 and 0.26 μg./L. respectively), in the dogs ventilated for the same period with ether/oxygen (Group I). It was considered that several obvious factors could have been partly responsible for the difference—struggling during induction with ether/air; a primary or secondary effect of the metabolic acidosis which was more pronounced in the ether/air group; and the possibility that the use of minimal thiopental and succinylcholine might "dampen down" sympathetic activity during anaesthesia with ether/oxygen, although neither drug had previously interfered with the measurement of increased plasma catecholamine levels in dogs subjected to a variety of stimuli (and in fact did not retard increases in plasma adrenaline in response to haemorrhage during ether/oxygen anaesthesia, as will be shown later). Other differences were that one group of animals was breathing spontaneously while the other was being ventilated artificially; and that arterial oxygen saturation, which was consistently 98–100 per cent during anaesthesia with ether/oxygen, averaged only 88 per cent after 45 minutes of ether/air (although it increased progressively thereafter). Finally, the factor considered to be of major significance was the difference in blood ether concentrations, which averaged 130 mg./100 ml. after 45 minutes of ether/air and only 84 mg./100 ml. after the same period of ether/oxygen.

Group III. The number of discrepancies between the first two experimental groups underlined the need for further studies. Table IV presents the averaged data obtained from six experiments in which dogs were ventilated for two hours with ether/oxygen under reasonably steady state conditions. Preliminary endotracheal intubation was performed in two animals under light thiopental anaesthesia, and in the other four experiments with the aid of intravenous succinylcholine alone, this subsequently being given as an infusion throughout every

TABLE IV

AVERAGED RESULTS (6 EXPERIMENTS) IN DOGS VENTILATED WITH ETHER/OXYGEN FOR TWO HOURS (GROUP III)

	pH	pCO_2 (mm. Hg)	Separated plasma standard HCO_3^- (mm./L.)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	Blood ether (mg./100 ml.)	Mean arterial blood pressure (mm. Hg)	Heart rate
—	7.48	27	19.2	0.12	0.22	—	133	99
+ 30′	7.37	31	17.2	0.52	0.44	143	120	179
+ 60′	7.33	30	15.6	0.93	0.58	154	102	169
+ 90′	7.27	33	15.0	1.0	0.89	152	105	155
+120′	7.23	33	13.8	1.7	1.1	153	103	162

study. The results demonstrate progressive rises in average plasma adrenaline and noradrenaline, a fall in pH and "separated plasma bicarbonate" attributable to a non-respiratory acidosis, an increase in heart rate, and a gradual reduction in arterial blood pressure. Table V shows the relevant statistical analysis of

TABLE V

ANALYSIS OF VARIANCE ON THE RESULTS OBTAINED DURING VENTILATION WITH ETHER/OXYGEN IN THE INTACT AND ADRENALECTOMIZED DOGS OF GROUP III

		Intact		Adrenalectomized	
Source of variation	Degrees of freedom	Adrenaline mean square	Noradrenaline mean square	Adrenaline mean square	Noradrenaline mean square
Control vs. 30′, 60′, 90′, 120′	1	4.2300*	1.2793†	0.0042	0.2623
Among samples during anaesthesia	3	1.4746	0.4674†	0.0447	0.1077
Between dogs	5	3.3684†	0.1310	0.0160	0.1872
Error	20	0.8032	0.0917	0.0298	0.1052

*$p < 0.05$
†$p < 0.01$

variance on the catecholamine data (intact dogs). Plasma noradrenaline showed highly significant increases over control samples at all times after 30 minutes of ether anaesthesia ($p < 0.01$), while a greater variability in adrenaline response is shown by the fact that increases were significant statistically only when the control samples were compared with those after two hours of ether anaesthesia ($p < 0.05$).

In this group of intact animals (Table IV) a direct and significant relationship ($p < 0.01$) could be shown between total catecholamine and blood ether concentrations (Fig. 1). Figure 2, from one experiment, illustrates the effects on arterial pH, plasma catecholamines, and mean arterial blood pressure, of ventilation with ether/oxygen to blood levels of ether which are at the upper limit of, and above, the clinical range.

Comparison of the results given in Tables III and IV shows that the metabolic acidosis accompanying spontaneous breathing of ether/air was more severe than that induced by ventilation with ether/oxygen, at roughly comparable times, even though blood ether levels were higher in the latter group. A lower arterial oxygen saturation may be partly responsible for this, and for the somewhat

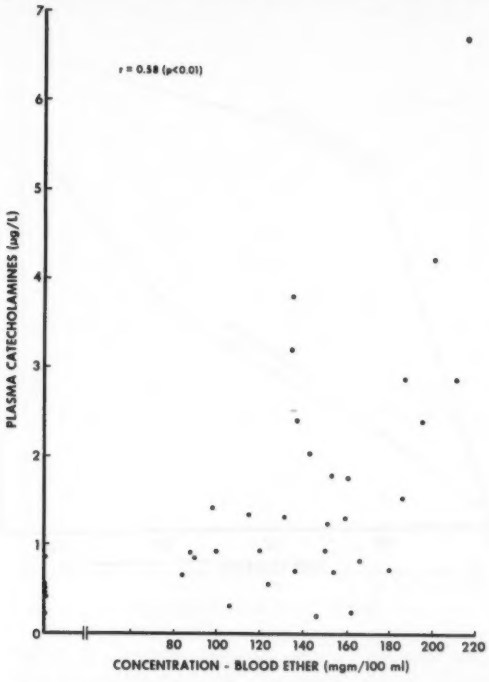

FIGURE 1. Relation between total plasma catecholamines and blood ether concentrations during ether anaesthesia in six intact dogs (Group III).

higher plasma catecholamine levels in the ether/air group, but the differences may also be related to increased muscular activity involved in the spontaneous response of this group of animals to an increased "respiratory drive" induced by diethyl ether.

Figure 3, from the data obtained in the ether/oxygen group of dogs (average results in Table IV), illustrates the highly significant ($p < 0.001$) inverse correlation between the levels of plasma adrenaline and "separated plasma bicarbonate"; this confirms a relationship previously suggested by Brewster and colleagues.[26]

In an attempt to identify the source of the noradrenaline liberated in the dog during ether anaesthesia, six animals were adrenalectomized bilaterally and after a rest period of about 45 minutes were ventilated with ether/oxygen for two hours. The results are shown in Table VI. Average blood ether levels at each time interval were lower than in the comparable group of intact dogs (see Table IV), which to some extent affects close comparisons of the two groups. As was expected following adrenalectomy, plasma adrenaline failed to increase during ether anaesthesia. Plasma noradrenaline showed small or moderate rises, but because of variability the response was insignificant statistically. Figure 4 compares the adrenaline and noradrenaline levels in the intact and adrenalectomized

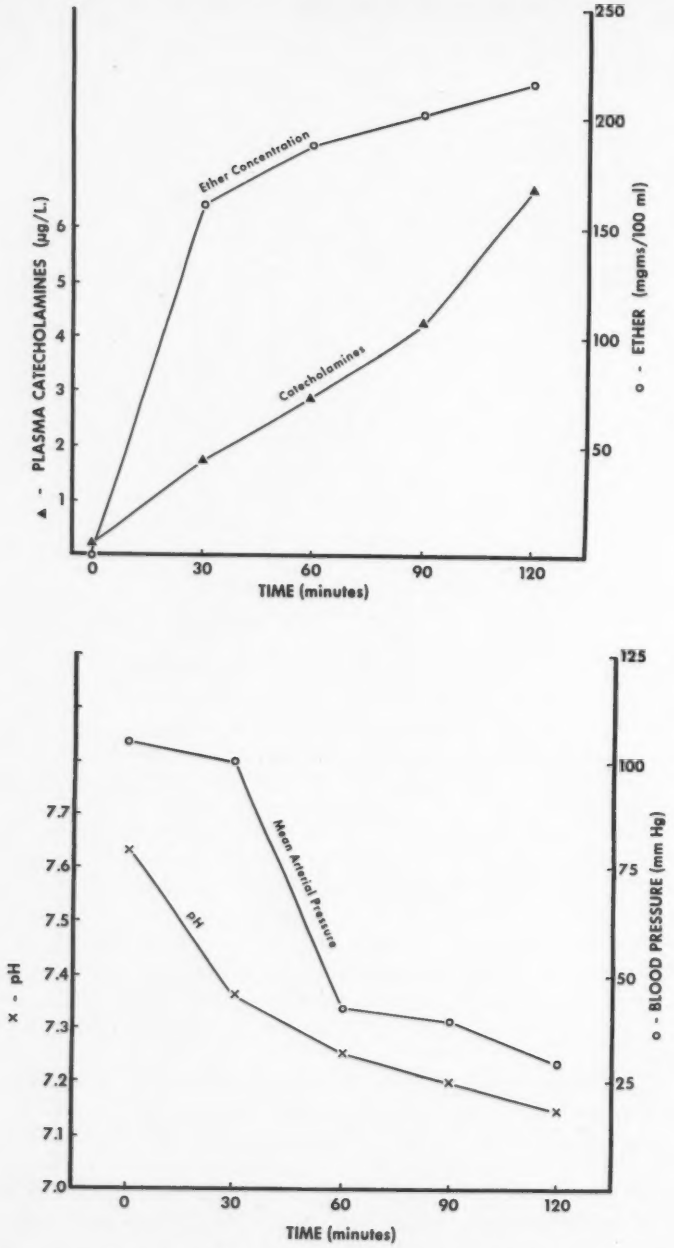

FIGURE 2. Arterial pH, total plasma catecholamines, blood ether concentrations, and mean arterial blood pressure changes in one animal study during ether/oxygen ventilation (Group III).

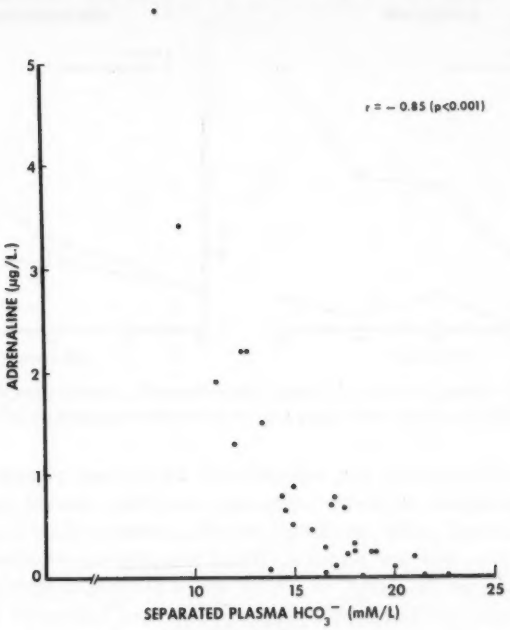

FIGURE 3. Relation between plasma adrenaline and "separated plasma standard bicarbonate" during ether/oxygen ventilation of intact dogs (Group III).

TABLE VI

AVERAGE RESULTS IN ADRENALECTOMIZED DOGS (6 EXPERIMENTS) VENTILATED WITH ETHER/OXYGEN (GROUP III)

	pH	pCO_2 (mm. Hg)	Separated plasma standard HCO_3^- (mM./L.)	Adrenaline (µg./L.)	Noradrenaline (µg./L.)	Mean arterial blood pressure (mm. Hg)	Heart rate	Blood glucose (mg./100 ml.)	Blood ether (mg./100 ml.)
—	7.48	24	18	0.10	0.25	121	165	74	—
+ 30′	7.46	26	18	0.04	0.36	109	174	75	113
+ 60′	7.41	28	17	0.21	0.48	104	160	74	128
+ 90′	7.40	28	17	0.08	0.41	88	159	74	137
+120′	7.37	28	16	0.20	0.67	86	170	67	135
20% CO_2	6.79	160	19	0.42	1.6	51	168	89	151

animals ventilated with ether/oxygen--the pCO_2 levels were very similar, as shown in Tables IV and VI. In the dog anaesthetized with diethyl ether release of noradrenaline occurs partly from extra-adrenal areas. Because blood ether levels were lower in the adrenalectomized animals, it is possible that at equivalent anaesthetic concentrations extra-adrenal release of noradrenaline would be proportionately greater than is shown in Figure 4.

Following this two-hour period of ventilation with ether/oxygen in adrenal-

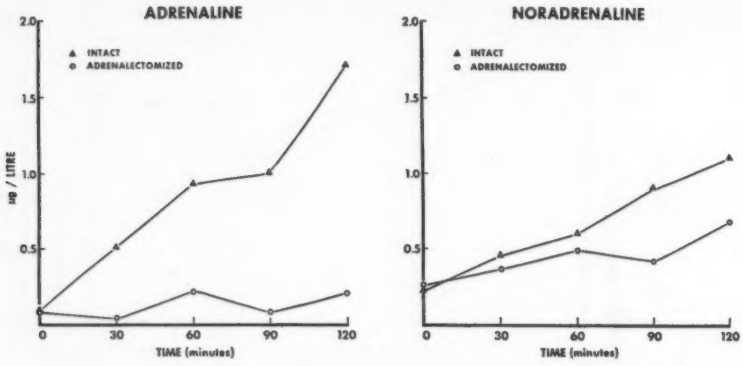

FIGURE 4. Average values of plasma adrenaline and noradrenaline during ether/oxygen ventilation in six intact dogs and six adrenalectomized dogs (Group III).

ectomized dogs, hypercarbia was induced with 18 per cent carbon dioxide/oxygen /ether. The immediate circulatory response to carbon dioxide was usually a fall in mean arterial and pulse pressures; systolic pressure then increased, but fell gradually over the next few minutes. Blood samples were withdrawn after 8 to 14 minutes (average 10 min.), at which times systolic and diastolic pressures were both reduced, while plasma noradrenaline was increased to levels significantly higher ($p < 0.05$) than those induced by ether anaesthesia alone (Table VI). The further increase in blood ether concentration (average 16 mg./100 ml.) resulting from this 10-minute period of hypercarbia should be noted, since this might explain in part a further increase in plasma noradrenaline concentration. However, no significant correlation could be established between total catecholamine and blood ether levels during the preceding two hours of ether anaesthesia (in the adrenalectomized animals, see Table XIII). Furthermore, at almost identical average blood ether concentrations plasma noradrenaline was higher during hypercarbia in adrenalectomized dogs than at normal pCO_2 in the intact animals. Thus, it is considered that the increases in plasma noradrenaline as a result of ventilation with carbon dioxide were too great to be affected, except to a minor degree, by the relatively small increase in blood ether concentration.

Comparison of the acid-base data in Table IV (intact) and Table VI (adrenalectomized) shows that adrenalectomy greatly reduced the metabolic acidosis induced by ether anaesthesia in the dog. This can be further demonstrated by pCO_2/pH plots (semi-logarithmic scale) for blood samples withdrawn before and after two hours of ether anaesthesia (Fig. 5). In intact dogs the points for samples withdrawn at the end of this period of anaesthesia lie to the left (acid side) of those for control samples. Since the "control" and "anaesthesia" pCO_2 levels did not differ significantly, this indicates the existence of a metabolic acidosis after two hours of ether anaesthesia. In the adrenalectomized animals the difference is much smaller. A comparison of the changes in "separated plasma bicarbonate" before and after two hours of ether anaesthesia in intact and adrenalectomized animals shows a significantly more marked ($p < 0.05$) metabolic

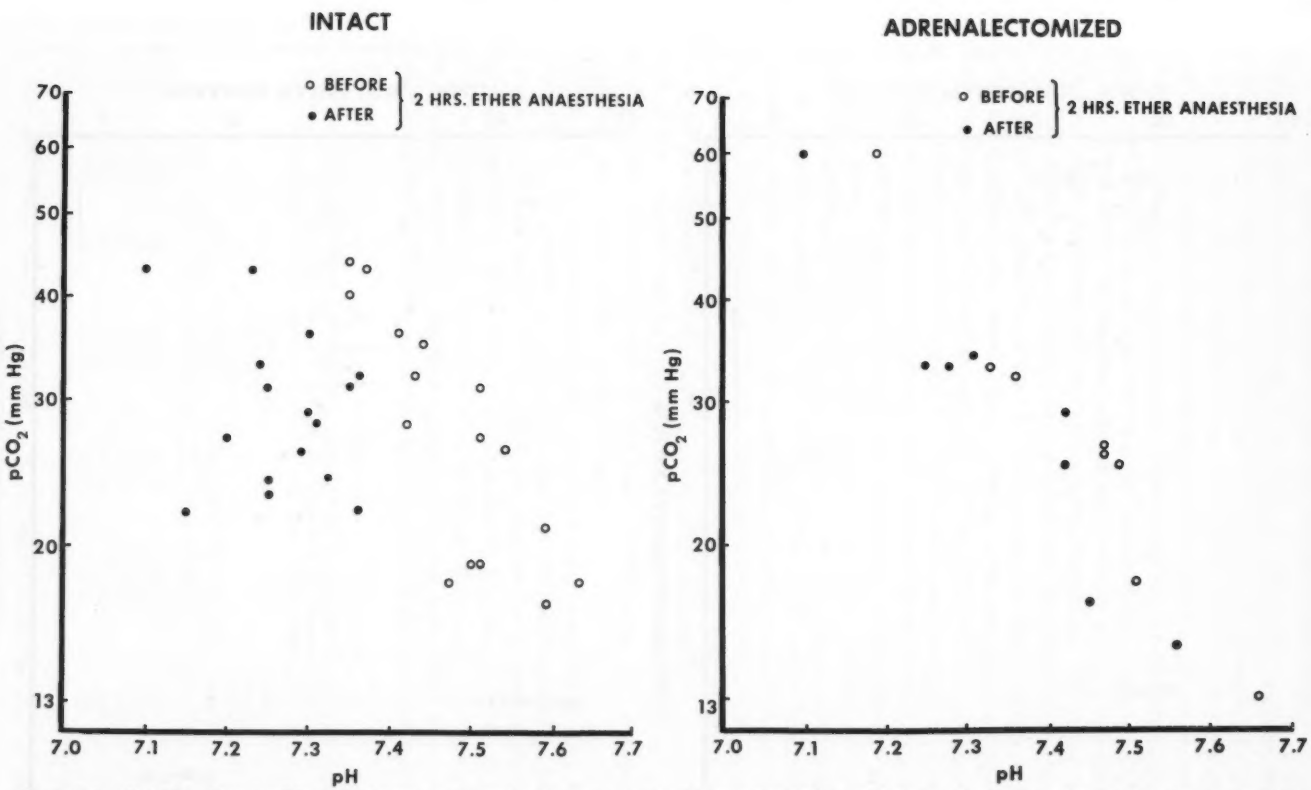

FIGURE 5. Relationship of pCO_2 (logarithmic scale) and pH of arterial blood samples withdrawn before and after two hours' ether/oxygen ventilation in 16 intact dogs and 8 adrenalectomized dogs. (Studies of Group III, and 12 other experiments the additional data from which is not included in this report.)

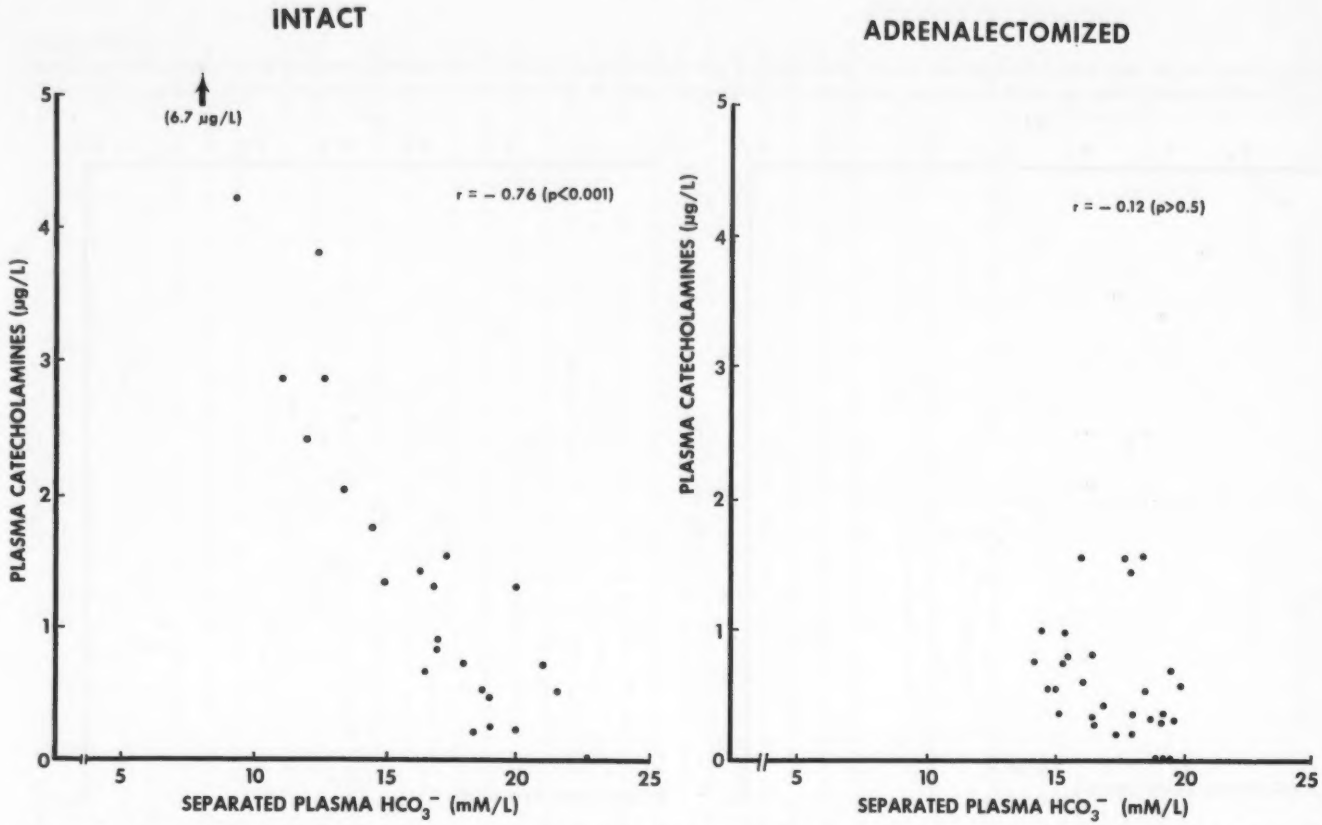

FIGURE 6. Relation of total plasma catecholamines and "separated plasma standard bicarbonate" during ether/oxygen ventilation in intact and adrenalectomized dogs (Group III).

acidosis in the intact animals. Figure 6 contrasts the relationship between total catecholamine concentration and "separated plasma bicarbonate" in the intact with that in the adrenalectomized dogs anaesthetized with ether; in the intact group a highly significant inverse correlation ($p < 0.01$) could be demonstrated, but not in the adrenalectomized animals. Blood sugar levels in the adrenalectomized dogs showed little or no change during ether anaesthesia at normal pCO_2 (Table VI), by comparison with the increases known to occur in intact animals.[27]

Control blood pressures and heart rate were respectively lower and higher in the adrenalectomized than in the intact dogs, but the difference in the degree of change induced by ether in the two groups was less than expected. Thus, in the intact animals mean arterial bood pressure after two hours of ether anaesthesia (average blood ether concentration 153 mg./100 ml.) was reduced by 23 per cent of the control value, while in the adrenalectomized dogs (average blood ether 135 mg./100 ml.) the reduction was by 29 per cent of control. This indicates that serious circulatory impairment is not a necessary accompaniment of moderately deep ether anaesthesia in adrenalectomized dogs. Percentage changes in mean arterial blood pressure in the adrenalectomized dogs show a highly significant negative correlation ($r = -0.701$, Table XIII) with blood ether concentrations, during two hours of anaesthesia. A similar analysis in the intact dogs of the same group shows that for blood ether levels below 180 mg./100 ml. there is no correlation of significance ($r = 0.143$); when the seven values above this level are included correlation becomes more definite ($r = -0.565$), from which it can probably be inferred that at very high blood ether concentrations release of catecholamines from the adrenal medulla does not antagonize the circulatory depressant action of diethyl ether.

Group IV. As was shown in Table I, and contrary to studies in man by other workers[28,29] cyclopropane anaesthesia in dogs was not associated with convincing increases in plasma noradrenaline. This was reinvestigated and confirmed at a later date in a group of six dogs ventilated for 90 minutes with 25–30 per cent cyclopropane in oxygen (induction with minimal thiopental, no succinylcholine used). Small, statistically significant rises in plasma adrenaline were measured (Table VII), similar to those in the earlier group (Table I); this degree of increase

TABLE VII

AVERAGE RESULTS (6 STUDIES, GROUP IV) OF VENTILATION WITH 25–30 PER CENT CYCLOPROPANE IN OXYGEN, AND A FURTHER 20 MINUTES OF HYPERCARBIA

	pH	pCO_2 (mm. Hg)	Standard HCO_3^- (whole blood) (mM./L.)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	Mean arterial blood pressure (mm Hg)	Heart rate
Control	7.494	24	21.3	0.05	0.18	110	102
+15′	7.542	21	21.0	0.17	0.23	102	97
+45′	7.519	22	20.4	0.25	0.21	116	104
+90′	7.487	22	19.3	0.36	0.19	108	100
15% CO_2	6.949	108	14.6	1.7	1.1	88	140

is difficult to assess when considered with the small reduction in "whole blood standard bicarbonate," since both these effects could be a result of blood sampling

in these dogs, whose mean weight of only 7 kg. was well below the average for this laboratory. No significant changes in plasma noradrenaline were measured during cyclopropane anaesthesia.

It is emphasized that the "whole blood standard bicarbonate" determined in this group of experiments[30] is not necessarily influenced by changes in arterial pCO_2, the values representing the metabolic component of acid-base balance.

After 90 minutes of 25–30 per cent cyclopropane anaesthesia, heart rate and mean arterial pressure were almost unchanged from control values, although systolic pressure was reduced and diastolic increased.

When hypercarbia was induced by ventilation with 15 per cent carbon dioxide and 25 per cent cyclopropane in oxygen for 20 minutes, plasma adrenaline and noradrenaline both showed marked increases (Table VII). The average increase and the variability were both greater in the case of adrenaline, and the changes were not significant statistically. By comparison with the levels after 90 minutes of anaesthesia with "normal" pCO_2, noradrenaline was significantly increased after this 20-min. period of hypercarbia during cyclopropane anaesthesia ($p < 0.05$). The initial circulatory response to carbon dioxide was usually a fall in pulse and mean pressures, this being followed by a phase of increased systolic and lowered diastolic pressures. Heart rate was increased. After 20 minutes mean pressure was reduced, largely because of the reduced diastolic pressure.

The pronounced reduction in "whole blood standard bicarbonate," at an average pCO_2 of 108 mm. Hg, demonstrates that a metabolic acidosis was induced by hypercarbia during cyclopropane anaesthesia.

Other Observations on Haemorrhage, Hypercarbia, and Asphyxia

In a previous study it was shown that increases in plasma catecholamine levels in response to haemorrhagic hypotension and hypercarbia were not prevented during anaesthesia with oxygen and halothane (2 per cent or higher).[9] In the present studies, five dogs (from Group I) were subjected to a 20 ml./kg. haemorrhage during ventilation with ether/oxygen (blood levels averaging 100 mg./100 ml.). The data in Table VIII show that plasma adrenaline increased markedly in every instance, with minimal changes in noradrenaline. There is clearly no

TABLE VIII

PLASMA ADRENALINE AND NORADRENALINE LEVELS BEFORE AND AFTER HAEMORRHAGE (APPROXIMATELY 20 ML./KG.) IN 5 DOGS VENTILATED WITH ETHER/OXYGEN (GROUP I)

Before haemorrhage			After haemorrhage		
Mean arterial blood pressure (mm. Hg)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	Mean arterial blood pressure (mm. Hg)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)
119	0.37	0.18	83	1.6	0.26
127	0.60	0.12	65	2.2	0.36
163	1.2	0.36	60	7.6	0.84
115	0.56	0.95	33	5.9	1.0
128	0.99	0.23	90	3.5	0.32
130	0.74	0.37	66	4.2	0.56

evidence that diethyl ether impairs the sympatho-adrenal responses to haemorrhage; comparison with the values previously measured during light thiopental anaesthesia[2] could even favour an enhanced response during ether anaesthesia (although this could not be accepted without further studies). As shown earlier in this communication, hypercarbia induced noradrenaline release during ether anaesthesia in adrenalectomized dogs (Table VI) and increased the plasma levels of adrenaline and noradrenaline during cyclopropane anaesthesia in intact dogs (Table VII). Furthermore, pronounced increases in plasma adrenaline and noradrenaline occurred in response to asphyxia (hypoxia plus hypercarbia) during cyclopropane anaesthesia in one experiment (Table IX). In this study there was

TABLE IX

EFFECT OF 20 MINUTES OF "APNOEA IN AIR" (PRECEDING THE 45' SAMPLE) IN A DOG PREVIOUSLY VENTILATED WITH 50 PER CENT CYCLOPROPANE/OXYGEN (GROUP I)

	pH	pCO_2 (mm. Hg)	Separated plasma standard HCO_3^- (mM./L.)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	Oxygen saturation (percentage)
—	7.41	38	23.0	0.0	0.10	99
+15'	7.41	38	23.0	0.01	0.03	99
+45'	6.87	156	22.8	4.9	1.1	42
+90'	7.21	37	14.1	3.6	0.72	89

no measurable increase in plasma catecholamine concentration after 15 minutes of uncomplicated cyclopropane anaesthesia (concentrations up to 50 per cent). A period of acute asphyxia then followed, with the respirator disconnected and the animal left in apnoea with the endotracheal tube open to air. During the next 20 minutes arterial pH fell to 6.87, pCO_2 rose to 156 mm. Hg, oxygen saturation was reduced to 42 per cent, and plasma adrenaline and noradrenaline increased to 4.9 and 1.1 μg./L. respectively. Circulating catecholamine levels were still elevated after a subsequent 45-min. period of ventilation with 100 per cent oxygen (90-min. sample, Table IX), at which time arterial oxygen saturation was still reduced although pCO_2 had returned to normal. The low values for arterial pH and "separated plasma bicarbonate" measured after this period of ventilation reflect the severe metabolic acidosis which resulted from this episode of asphyxia. The findings show that serious physiological insults of this nature during general anaesthesia result in biochemical changes which are not necessarily rapidly reversed.

Ventricular arrhythmias were frequent during ventilation with oxygen and 50 per cent cyclopropane, a concentration which is not uncommonly employed in clinical anaesthesia. Whereas no animals died during anaesthesia with ether, chloroform, halothane, or cyclopropane in concentrations of 30 per cent or below, two animals died as a result of ventricular fibrillation after 45 and 57 minutes of ventilation with 50 per cent cyclopropane/oxygen (data excluded from Table I). In one dog a small rise in plasma adrenaline preceded ventricular fibrillation; the changes measured in the other animal were negligible. While electrocardiography frequently demonstrated supraventricular arrhythmias, persistent ventricular arrhythmias did not occur in any of the six dogs ventilated with 30 per

cent cyclopropane/oxygen at normal arterial CO_2 tensions, nor during the period of cyclopropane anaesthesia with hypercarbia (Table VII). In both cyclopropane groups (Tables I and VII) there was insufficient information to establish any relationship between cardiac arrhythmias and circulating catecholamines. Cardiac arrhythmias were noted frequently during anaesthesia with 50 per cent cyclopropane/oxygen without detectable increases in plasma adrenaline or noradrenaline, while the state of severe and prolonged asphyxia which occurred in one experiment (Table IX) did not result in ventricular fibrillation in spite of greatly increased levels of plasma adrenaline and noradrenaline.

Clinical Studies

Cyclopropane anaesthesia. Cyclopropane/oxygen was administered to a total of seventeen patients. The results were divided into those obtained during anaesthesia alone, and those while surgery was proceeding under cyclopropane anaesthesia. Data from six patients were rejected because of moderate respiratory acidosis present on most occasions when blood samples were withdrawn, and from two other patients because no acid-base data were available. The frequency of mild degrees of respiratory acidosis under average clinical conditions is shown by the finding that whereas pCO_2 levels were below 55 mm. Hg at all times in the remaining nine patients, in only five of them were the levels below 49 mm. Hg when samples were withdrawn during cyclopropane anaesthesia before surgery. There was no evidence to suggest any difference between plasma catecholamine levels at arterial pCO_2 49–55 mm. Hg and those below 49 mm. Hg, nor any discrepancy between the values measured during cyclopropane anaesthesia with manually assisted respiration and with mechanical ventilation (positive pressure only). The data from all nine patients are therefore included in the results shown in Table X. In two instances succinylcholine was used (in one case as a single dose prior to intubation and in the other as a continuous infusion).

TABLE X

ADRENALINE (A), NORADRENALINE (N), AND TOTAL (A + N) PLASMA CATECHOLAMINE CONCENTRATIONS BEFORE AND DURING ANAESTHESIA (WITH AND WITHOUT SURGERY). CYCLOPROPANE, 9 PATIENTS; DIETHYL ETHER, 16 PATIENTS; HALOTHANE, 11 PATIENTS. T-TEST APPLIED TO PAIRED SAMPLES (DIFFERENCES FROM CONTROL VALUES)

	Control			Anaesthesia			Anaesthesia + Surgery		
	A	N	Total	A	N	Total	A	N	Total
Cyclopropane	0.15	0.15	0.30	0.48	0.33	0.81†	0.26	0.58*	0.84†
Ether	0.13	0.26	0.29	0.26*	0.61†	0.87*	0.45†	0.68†	1.13†
Halothane	0.13	0.34	0.47	0.28	0.36	0.64	0.31*	0.38	0.70

*$p < 0.05$
†$p < 0.01$

Total plasma catecholamine concentration increased from an average control level of 0.30 μg./L., to 0.81 μg./L. after periods of cyclopropane anaesthesia ranging from 15 to 65 minutes. The increases were highly significant ($p < 0.01$). The average rise in plasma noradrenaline was small and statistically insignificant (Table X). However, convincing increases were measured in occasional patients (Table XI), in the absence of respiratory acidosis. Plasma adrenaline showed

TABLE XI

INCREASES IN PLASMA NORADRENALINE IN A PATIENT ANAESTHETIZED WITH CYCLOPROPANE, WITH FURTHER RISES (ALSO INVOLVING ADRENALINE) DURING THE PERIOD OF SURGERY

Time	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	pCO_2 (mm. Hg)	Arterial pressure S/D (mm. Hg)	Heart rate
—	0.23	0.03	41	140/90	84
+ 52′	0.43	0.86	37	140/100	60
Surgery					
+105′	0.33	1.3	39	140/98	60
+195′	1.2	2.0	54	140/86	56

INCREASE IN PLASMA NORADRENALINE, AND HYPERTENSION (ACCOMPANIED BY CARDIAC ARRHYTHMIAS) DURING RESPIRATORY ACIDOSIS IN A PATIENT ANAESTHETIZED WITH CYCLOPROPANE

Time	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	pCO_2 (mm. Hg)	Arterial pressure S/D (mm. Hg)	Heart rate
—	0.0	0.21	30	120/70	72
+20′	0.18	1.1	60	185/90	82
+35′	0.08	1.4	69	170/90	108

small, variable, and statistically insignificant increases during cyclopropane anaesthesia without surgery. The average levels were slightly greater than those of noradrenaline, and also of adrenaline during "cyclopropane anaesthesia with surgery" (Table X). This could be related to a failure to reach a steady state of anaesthesia; for example, laryngoscopy and endotracheal intubation were accomplished during the period of cyclopropane anaesthesia alone, and these manœuvres are known to be accompanied by autonomic responses.[31]

During cyclopropane anaesthesia with surgery, total plasma catecholamine concentration averaged 0.84 μg./L., the increase over control again being highly significant ($p < 0.01$). In this period average plasma noradrenaline (0.58 μg./L.) was also significantly ($p < 0.05$) higher than control (0.15 μg./L.). It was not possible in this group of patients to show any increase in plasma noradrenaline concentration with time, nor any significant difference between the total plasma catecholamine levels during cyclopropane anaesthesia and those during anaesthesia plus surgery; it is quite possible that the significant rise in plasma noradrenaline during "cyclopropane anaesthesia with surgery" was associated with progressive deepening of anaesthesia (that is, with increasing blood concentrations of cyclopropane), rather than with any effect attendant on operative interference.

Table XI shows the increases in plasma noradrenaline concentration which accompanied progressive respiratory acidosis in a patient anaesthetized with cyclopropane; respiration was assisted but inadequately so to the experienced observer. Arterial pressure was increased, ventricular arrhythmias were present at variable times throughout the administration, and respiratory depression with laryngeal spasm were troublesome during emergence from anaesthesia.

Halothane anaesthesia. Fourteen patients were anaesthetized with halothane; because of respiratory acidosis the data from two are excluded. In seven of the remaining twelve patients nitrous oxide/oxygen was used as the vehicle for vaporizing halothane/oxygen, and in the other five cases closed-circuit halothane was used throughout.[14] During the period of halothane anaesthesia without surgery total plasma catecholamine concentration was increased to an average of 0.64 μg./L. from a control level of 0.47 μg./L., a change which was insignificant (Table X). Although small increases in plasma adrenaline and noradrenaline were frequently measured, these were too variable for definite trends to be established. The total plasma catecholamine concentration during halothane anaesthesia plus surgery, 0.70 μg./L., was also insignificantly different from control. Average plasma noradrenaline during this period of surgery was not increased over the pre-anaesthetic level of 0.34 μg./L., but adrenaline showed small but significant increases ($p < 0.05$) to a level of 0.31 μg./L. (control, 0.13 μg./L.).

Ether anaesthesia. Ether anaesthesia was studied in nineteen patients, seventeen of whom were anaesthetized by one of us to ensure a reasonable consistency in technique. A semi-closed method with nitrous oxide/oxygen/ether was used for induction and endotracheal intubation, which was usually accomplished within 10 minutes (and invariably within 20 minutes); thereafter ether/oxygen was administered without rebreathing. A mild degree of oxygen limitation was found to be necessary for two or three minutes at the start of induction, and the data may be affected to a small extent by this and by the short period of nitrous oxide administration. Nevertheless, the technique is a realistic one which is still employed widely. Acid-base data were obtained in all but four cases, which were not excluded from consideration because of the rarity with which respiratory acidosis occurs during ether/oxygen anaesthesia without rebreathing (in our experience).

During ether anaesthesia highly significant increases in plasma noradrenaline were measured ($p < 0.01$), from an average control level of 0.26 μg./L., to 0.61 μg./L. after periods of anaesthesia ranging from 20–65 minutes (Table X). Plasma adrenaline showed smaller, but significant ($p < 0.05$), increments to an average of 0.26 μg./L., from a control of 0.13 μg./L. Ether anaesthesia plus surgery was also associated with an increased plasma noradrenaline level (average 0.68 μg./L.), and with a further rise in adrenaline (to an average of 0.45 μg./L.), the difference from the respective control value with each amine being highly significant ($p < 0.001$).

Table XII presents the data from a group of ten patients anaesthetized in an

TABLE XII

AVERAGE RESULTS OF 10 PATIENTS ANAESTHETIZED WITH ETHER/OXYGEN (DURING A PERIOD OF ONE HOUR PRIOR TO SURGERY)

	pH	pCO_2 (mm. Hg)	Standard HCO_3^- (mM./L.)	Adrenaline (μg./L.)	Noradrenaline (μg./L.)	Mean arterial pressure	Heart rate
Control	7.411	35.4	23.05	0.11	0.28	105	76
15–30′	7.378	36.3	21.30	0.33	0.62	105	92
40–60′	7.403	34.8	21.98	0.22	0.62	99	91

identical fashion with semi-closed nitrous oxide/oxygen/ether (for a period of 10–20 minutes), followed by ether/oxygen for periods up to 65 minutes, without surgical intervention. An accurate assessment of non-respiratory acid-base changes was attempted by using the measurement of whole blood "standard

TABLE XIII

CORRELATION COEFFICIENT (r) VALUES FOR VARIABLES MEASURED DURING ETHER ANAESTHESIA (SEE TABLES IV AND VI, AND TEXT)

	Total amines	Adrenaline	Noradrenaline	Percentage change in mean arterial pressure
Ether Concentration				
Intact dogs	0.582†	0.467*	0.164	−0.565†
Adrenalectomized dogs	0.132	—	—	−0.701†
Humans	0.652†	0.090	0.760†	—
Change in HCO_3^-				
Intact dogs	−0.760†	−0.847†		
Adrenalectomized dogs	−0.119	—		
Humans	0.021	0.097		

*$p < 0.05$
†$p < 0.01$

bicarbonate."[18,30] Table XII shows that a small but definite (and significant, $p < 0.01$) reduction in "standard bicarbonate" occurred during ether anaesthesia. The greater fall (1.8 mM./L.) was measured after the induction period, and could therefore be associated with the use of nitrous oxide. The level later showed some return toward the pre-anaesthetic value. Comparison of plasma adrenaline and "whole blood standard bicarbonate" levels, at both periods (Table XII), failed to show significant correlation. During ether anaesthesia arterial pressure showed little change, but there were incerases in heart rate and highly significant rises in plasma noradrenaline ($p < 0.01$), with smaller increases in the level of adrenaline (which were also significant, $p < 0.05$). From Figure 7 (data from four patients of Table XII) a direct correlation of increases in plasma noradrenaline with ether concentration is evident. The coefficient of correlation ($r = 0.760$) is significant ($p < 0.05$); but the number of observations is too small to allow a definite conclusion.

DISCUSSION

While the output of transmitter substance (noradrenaline) at adrenergic nerve endings probably bears a direct relationship to the rate of sympathetic stimulation, certain pharmacological agents have been shown to affect the amounts of transmitter released at a given rate of stimulation.[32] The interpretation of this is that release and destruction are intimately related at sympathetic receptor sites. When the adrenergic receptors are "occupied" by adrenergic blocking drugs such as dibenzyline, metabolic transformation of transmitter substance is interfered with and the plasma concentration rises. In a previous study, for example, it was shown that plasma noradrenaline levels in adrenalectomized dogs subjected to haemorrhage were much higher if the animals were pre-treated with dibenzyline;[4] in this instance the increased noradrenaline "release" could not be accounted

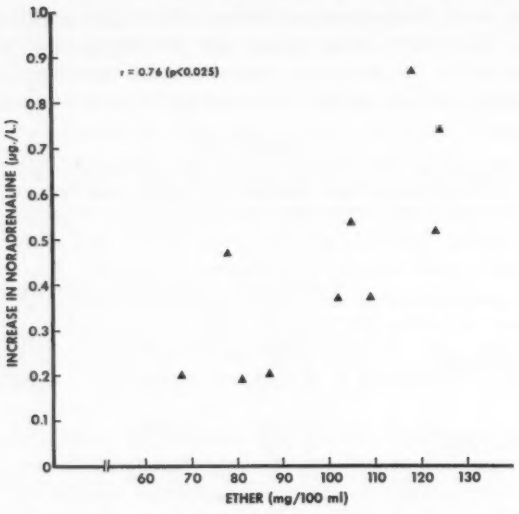

FIGURE 7. Relation between increases in plasma noradrenaline and blood ether concentrations in four patients during ether/oxygen anaesthesia (average duration one hour), prior to surgery.

for solely on the basis of a higher rate of sympathetic nervous discharge than was occurring in the untreated animals. A similar effect may occur with other adrenergic blocking drugs. These experimental observations are emphasized because they show that blockade of the effects of endogenously released catecholamines can be accompanied by increases in the levels circulating in the blood stream. On the basis of infusion experiments it has been deduced that general anaesthetic agents are unlikely to have any such effect;[33] however, metabolic breakdown of catecholamines administered by exogenous infusion or liberated from the adrenal medulla appears to be carried out in the liver by catechol O-methyltransferase,[34] whereas local transformation of catecholamines released in the tissues may involve mono-amine oxidase,[35] so that the effect of anaesthetics on the disposal of locally released transmitter is not necessarily the same as that on material infused exogenously or from the adrenal medulla.

In attempting some interpretation of the present studies, it has been necessary to assume that measurement of increased plasma catecholamine concentrations implies an increased rate of sympathetic discharge. In the absence of convincing evidence to the contrary this assumption is probably valid, but might require modification at a later date.

It is not known whether increased plasma catecholamine levels during ether anaesthesia result from direct sympathetic excitation, or whether they can be regarded as a compensatory phenomenon related to the direct myocardial and vasomotor depressant properties of diethyl ether. It has been suggested that activation of the ascending reticular formation occurs during light ether anaesthesia,[36] but more complete confirmation is required.[37] Hypersynchronous, seizure-

like activity in rhinencephalic structures (including the posterior hypothalamus) has been reported during certain phases of ether anaesthesia,[38] while depletion of noradrenaline from the hypothalamus also occurs.[39] These and other experimental observations point to an increase in subcortical neuronal activity during various stages of ether anaesthesia, but it clearly is not yet possible to describe the neurophysiological actions of diethyl ether in simple terms of "stimulation" or "depression."

The view of catecholamine responses as a vital reflex mechanism in the maintenance of homeostasis during ether anaesthesia is supported by the experiments of Brewster and associates,[40] who considered that direct depression of cardiac and vascular muscle was antagonized quantitatively by release of adrenaline and noradrenaline at rates of liberation approximating 1 μg./kg./min. In the present studies the highest total plasma catecholamine level measured during ether anaesthesia was 11 μg./L. in a dog breathing ether/air, so that the circulating concentrations were much lower than would result from this rate of liberation. It is probably not possible to draw comparisons on a quantitative basis, between the actions of infused catecholamines and those of adrenergic nerve stimulation (as a result of which only small quantities of transmitter will reach the circulation).

Although in the present study arterial pressure tended to fall progressively during ventilation with ether/oxygen in adrenalectomized dogs (from control levels which were lower than in intact animals), there was no convincing evidence of impending circulatory collapse at blood levels as high as 130 mg./100 ml. Several studies have demonstrated that the function of the sympathetic nervous system is essential for maintenance of normal circulation during ether anaesthesia,[40,41] but it is difficult to consider adrenal medullary liberation of catecholamines as a vital component of the reflex response to ether anaesthesia. It appears very probable, also, that "peripheral" sympathetic stimulation during ether anaesthesia in dogs is less than maximal, because superimposed hypercarbia resulted in considerably higher plasma noradrenaline levels in the adrenalectomized animals. The possibility must be considered, in this connection, that an increased pCO_2 or reduced tissue pH could affect the rate of diffusion from, and breakdown at, the site of release. Also pertinent to the peripheral sympathomimetic effects of ether is the rise in blood sugar during hypercarbia in the adrenalectomized dogs, which could be due to an increase in sympathetic activity above that produced by ether alone, although carbon dioxide can probably liberate glucose by a direct action on hepatic cells.[42]

Burn and Rand[43] have suggested that the "role" of adrenal medullary noradrenaline may be the replenishment of noradrenaline in depleted peripheral "stores." The fact that acutely adrenalectomized dogs can withstand at least two hours of moderately deep ether anaesthesia, and other stresses such as severe carbon dioxide accumulation,[6] is in keeping with a concept such as this, which relegates adrenal medullary noradrenaline to a secondary position.

The functions of the "neural" (extra-adrenal) and "humoral" (adrenal medullary) elements of the sympathetic nervous system should probably be clearly differentiated. At the same rates of electrical stimulation it was shown that the neural component produced effects many times greater than those elicited

by adrenal medullary secretion.[44] It seems more than probable that the "significance" of an increased circulating level of adrenaline and noradrenaline lies less with the effects induced indirectly via the blood stream on organs such as the heart, than with the fact that it is a manifestation of generalized sympathetic excitation, the more important component of which is an intimate liberation of noradrenaline at adrenergic nerve endings. At these sites the effect of released transmitter substance on local vasomotor tone or on cardiac rate and rhythm is much more intense than that of equivalent amounts carried by the blood stream.[44] The measurement of increased plasma levels of noradrenaline during ether anaesthesia in adrenalectomized dogs presumably implies widespread release from sympathetic nerve endings. Information is required concerning the liberation of noradrenaline from the heart[45] and brain[39] during general anaesthesia.

Many effects of ether anaesthesia in the dog are similar to those of adrenaline.[25] The significant inverse correlation between plasma catecholamine concentration and "separated plasma standard bicarbonate" established in intact dogs in the present study confirms the close interdependence of sympatho-adrenal excitation and metabolic acidosis during ether anaesthesia,[26] this being further demonstrated by a lesser degree of acidosis in the adrenalectomized animals. It is apparent from our findings and those of Brewster[26] that minimal acid-base (and plasma catecholamine) changes occur even in intact dogs at blood ether levels below about 100 mg./100 ml. At higher levels of blood ether acid-base changes still occur to some effect after total sympathetic blockade.[26] It has been suggested that a direct action of ether is involved, this being enhanced by adrenalectomized animals by peripheral sympathetic stimulation and extra-adrenal noradrenaline release. This appears more probable than an effect of diminished tissue perfusion or anoxia which although certain to be followed by a metabolic acidosis[46] could hardly account for the changes measured in the adrenalectomized dogs in the present study—there was no serious circulatory impairment at blood ether levels of about 130 mg./100 ml., and oxygenation was fully maintained. It is possible that noradrenaline may to some extent stimulate anaerobic carbohydrate metabolism, although there is evidence against this.[47] The severe metabolic acidosis in the dogs breathing ether/air (average blood levels 130 mg./100 ml.), which also showed a reduced arterial oxygen saturation, suggests the enhancement of acid-base changes by mild anoxia; this may be of some concern in view of recent attempts to revive the use of air rather than oxygen in anaesthetic mixtures.[48,49]

Clinical observations reveal the marked respiratory stimulation evoked by adrenaline injected subcutaneously during ether anaesthesia in man. It is conceivable to consider a relationship between the fact that pulmonary ventilation is well maintained during ether anaesthesia and the following experimental findings: impulse conduction through the lateral reticular formation is still maintained after ether anaesthesia is established;[50] discharges from respiratory nerve cells are maximal in the lateral reticular region;[51] and activation of the reticular system is readily induced by adrenaline and noradrenaline.[52] Respiratory activity, and that of nerve cells in the brain stem closely concerned with cardiovascular control, may well be affected by, and maintained at a high level under the influence of, endogenously released catecholamines. Thus a self perpetuating

cycle of reciprocal activation could occur, involving catecholamine release and central excitation.

It is of interest to note that in our studies the circulating noradrenaline concentration measured during ether anaesthesia in man was of the same order as that in adrenalectomized dogs, at roughly similar blood ether concentrations. It appears, moreover, that noradrenaline release in man during ether anaesthesia could occur largely from areas outside the adrenal gland,[33,53] although we have no studies to demonstrate this. Since the findings from the present study were that small increases in plasma adrenaline occurred in man, together with a mild metabolic acidosis, our data would be quite compatible with the assumption that the responses to ether anaesthesia in the dog and man are similar qualitatively if not quantitatively. The outstanding difference is apparently an exaggerated response of the adrenal medulla in dogs. Other evidence suggests that adrenal medullary discharge during ether anaesthesia is minimal or absent in man,[33,53] but it is difficult to believe that an agent which induces an increased discharge rate in sympathetic nerves would not sometimes release adrenal medullary hormones.

The fact that the adrenal medulla is more responsive, or is stimulated to a greater extent, in the dog, suggests that in this species the "humoral" component of the sympathetic nervous system is of more physiological "importance" than in man, whose peripheral autonomic control has probably developed to a greater extent because of the need to maintain circulation in the upright position.

In general the impression is left that the sympatho-adrenal excitation induced by diethyl ether occurs because of a direct or "irritant" action of ether itself, probably in the central nervous system. This may involve any nerve cells in the brain stem, or spinal cord[25] which can influence the rate of efferent sympathetic discharge. An effect on chemoreceptors[54] might be a factor of importance, while "chemical" excitation of the adrenal medulla[55] cannot be entirely rejected. This does not in any way refute the part played by the sympathetic nervous system in maintaining circulatory homeostasis in the face of direct myocardial depression, but the fundamental compensatory mechanisms operating under the influence of ether probably closely resemble those occurring during the administration of other non-hypotensive anaesthetic agents. From the significant direct correlation demonstrable between blood ether and total catecholamine concentrations in dogs (and from suggestive findings in relation to plasma noradrenaline in man), it could be implied that the response of the sympathetic nervous system during ether anaesthesia bears a quantitative relationship not necessarily to the degree of myocardial or vascular depression, but to the blood ether concentration. The pronounced increases in plasma catecholamine levels measured in dogs at blood ether concentrations above 180 mg./100 ml. are clearly unable to antagonize the severe hypotension encountered at such excessively deep levels of anaesthesia.

Since plasma noradrenaline did not show significant increases during cyclopropane anaesthesia in the dog, it appears that widespread sympatho-adrenal excitation is not induced by cyclopropane in this species. It is considered that while the rather small increases in plasma adrenaline could be an effect of cyclo-

propane it is more likely that they represent adrenal medullary stimulation from blood sampling or "experimental stress." Blood pressure was reduced by concentrations of 50 per cent cyclopropane when given continuously, but in spite of experimental evidence in animals and man to show that many circulatory reflexes are not greatly modified during cyclopropane anaesthesia,[1] it appears that sympatho-adrenal activation is not a "physiologically essential" component of the homeostatic mechanisms operating during anaesthesia with this agent. This seems to cast further doubt on the likelihood of sympatho-adrenal stimulation being "compensatory" during ether anaesthesia.

The results of several clinical studies suggest a heightened degree of sympathetic[28] and parasympathetic[56] tonus during cyclopropane anaesthesia in man. The data from the present study also indicate that cyclopropane anaesthesia can be accompanied by noradrenaline release in man, but the response appears to be variable. In our studies diethyl ether produced more consistent and definite changes. Differences in the data obtained with these two agents, and between different laboratories, could be at least partly associated with variations in pulmonary ventilation, which in the present study was assisted or controlled in every patient anaesthetized with cyclopropane, whereas this was found to be unnecessary during ether anaesthesia.

Splanchnic and renal vasoconstriction occur during cyclopropane anaesthesia,[57] and there is an increase in central venous pressure.[58] In a recent study[56] cardiac output was increased, together with total peripheral resistance (calculated from the data). These could be relatively independent manifestations of central sympathetic excitation, but it could also be suggested that a primary effect of cyclopropane might be an increase in vascular tone—it has been stated that vascular sensitivity to catecholamines is enhanced by anaesthetic concentrations of cyclopropane.[1] As a result of increased vascular resistance, and because of well-maintained reflex mechanisms, there could be a "compensatory" increase in cardiac force of contraction. Arrhythmias would be liable to occur because of increased noradrenaline release and cardiac work, particularly if cyclopropane sensitized cardiac muscle. As the blood concentration of cyclopropane fell at the end of administration, cardiac force would be lessened, the increased vascular tone reduced, and a ready explanation for cyclopropane "shock" would be available; the whole picture would be intensified by respiratory acidosis, a reduced circulating blood volume, effects of movement, reduction in arterial oxygen saturation, and so on.[59]

Plasma concentrations of noradrenaline might be increased during cyclopropane anaesthesia as a result of liberation of transmitter substance at adrenergic nerve endings concerned with regulation of vascular tone, with a small contribution from cardiac sympathetic nerves. It would be interesting to know whether an increased plasma noradrenaline concentration occurs predominantly in those patients who show a high peripheral resistance and an increased cardiac stroke volume. Also, more information is needed about the possibility of a primary sensitizing effect of cyclopropane to normal amounts of sympathetic transmitter substance liberated at nerve terminals within the heart. Cardiac arrhythmias during cyclopropane anaesthesia are not readily explicable only on a basis of

increased noradrenaline release from nerve-endings within the heart, since this almost certainly also occurs during ether anaesthesia, which is rarely accompanied by ventricular arrhythmias.

The fact that plasma catecholamine levels are not significantly increased during uncomplicated halothane anaesthesia in man or dogs suggests that sympathetic responses are not directly excited by this agent. Studies reported previously showed that halothane does not effectively block the catecholamine responses to haemorrhage and hypercarbia in dogs,[9] although without more extensive comparative studies with other agents it can not be affirmed that some reduction does not occur. There is some evidence to suggest that the catecholamine responses to hypercarbia during halothane anaesthesia in man are less marked than during anaesthesia with cyclopropane.[60] Such comparisons are difficult to interpret without more detailed knowledge of "levels" of anaesthesia, in neurophysiological terms. The studies reported here seem to indicate that reflex or direct sympatho-adrenal responses to haemorrhage, asphyxia, and hypercarbia are well maintained during anaesthesia with diethyl ether and cyclopropane.

Because of losses in recovery of catecholamines from plasma, and other problems in methodology, it is considered that increases in plasma catecholamine levels during general anaesthesia are in reality greater than indicated, while it is probable that minimal changes have frequently gone undetected.

Finally, it is necessary to emphasize the wide variations encountered in both dogs and patients, and it should be noted that statistical inferences indicate *probabilities*; thus, while changes in plasma catecholamine concentrations are less likely to occur during anaesthesia with halothane than with ether or cyclopropane, their occurrence at any time in any individual patient is not precluded.

Summary

Plasma catecholamine levels were studied during general anaesthesia with diethyl ether, cyclopropane, and halothane in dogs and human subjects. Anaesthesia with ether/oxygen caused highly significant increases in plasma noradrenaline in dogs and man. The response was less marked in man, but a significant direct correlation could be established (in a small number of patients) between the rise in plasma noradrenaline and blood ether concentrations during ether anaesthesia without surgical interference. Plasma adrenaline was also significantly increased in dogs during ether anaesthesia, and in man to a lesser extent; highly significant rises were measured during surgery in man. The severe metabolic acidosis induced by diethyl ether in the dog bore a direct relationship to circulating catecholamine concentration and was greatly reduced by bilateral adrenalectomy. A mild but definite metabolic acidosis was measured during nitrous oxide/oxygen/ether and ether/oxygen anaesthesia in man. In adrenalectomized dogs, variable moderate rises in plasma noradrenaline were measured during ether anaesthesia, from which it is inferred that in this species the rise in plasma noradrenaline stems partly from extra-adrenal areas. Since hypercarbia superimposed on ether anaesthesia in adrenalectomized dogs caused further increases in plasma noradrenaline, it is considered that the extra-adrenal sympathetic excitation induced by ether is submaximal.

Cyclopropane anaesthesia in dogs with normal pCO_2 was accompanied by very small increases in plasma adrenaline, probably accounted for by blood sampling. In man, cyclopropane anaesthesia was associated with a significant increase in total plasma catecholamine concentration, with definite rises in plasma noradrenaline in certain patients at both normal and raised levels of arterial pCO_2, the increases at normal pCO_2 becoming significant statistically only as a result of deeper anaesthesia, because of an effect of surgery, or both.

Halothane did not produce significant increases in plasma catecholamine concentration in dogs or man, although plasma adrenaline was significantly increased during surface surgery under halothane anaesthesia in man.

Elevated plasma catecholamine levels as a result of haemorrhage during ether anaesthesia, hypercarbia and asphyxia during cyclopropane anaesthesia, and hypercarbia during ether anaesthesia in adrenalectomized dogs, together with studies previously reported, indicated that the currently used general anaesthetic agents do not have any major "dampening" effect on the sympatho-adrenal responses to the common forms of stimulation encountered in the operating room.

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Résumé

Nous avons étudié chez des chiens et chez des humains, au cours de l'anesthésie générale à l'éther, au cyclopropane et à l'halothane, les variations du taux de catécholamine dans le plasma. L'anesthésie à l'éther et oxygène a entraîné une augmentation importante du taux de noradrénaline dans le plasma aussi bien chez les chiens que chez l'homme. Chez l'homme, la réponse était moins marquée, mais on a pu établir une corrélation directe (chez un petit nombre de malades) entre l'augmentation du taux de noradrénaline dans le plasma et la concentration du sang en éther au cours de l'anesthésie à l'éther sans chirurgie. Le taux d'adrénaline dans le plasma était également augmenté de façon importante chez les chiens au cours de l'anesthésie à l'éther, mais chez l'homme, à un degré moindre; au cours de la chirurgie on a également observé des augmentations considérables. L'acidose métabolique marquée produite par l'éther chez le chien est directement proportionnelle au taux de catécholamine circulant, et elle a été considérablement réduite par la surrénalectomie bilatérale. Nous avons également dépisté, chez l'homme, au cours de l'anesthésie au protoxide/oxygène/éther, et au cours de l'anesthésie à l'éther/oxygène, une acidose légère mais positive.

Chez les chiens surrénalectomisés, nous avons observé une augmentation légère et variable du taux d'adrénaline dans le plasma, au cours de l'anesthésie

à l'éther, ce qui nous incite à croire que, chez cet animal du moins, l'augmentation du taux d'adrénaline dans le plasma provient, en partie, d'endroits autres que la surrénale. Etant donné que si l'on ajoute l'hypercarbie à l'anesthésie à l'éther, chez des chiens surrénalectomisés, l'on observe une augmentation additionnelle du taux de noradrénaline dans le plasma, l'on est porté à croire que l'excitation sympathique extrasurrénalienne produite par l'éther est une excitation probablement submaximale.

Au cours de l'anesthésie au cyclopropane, chez des chiens conservant un P CO_2 normal, l'on a constaté de légères augmentations du taux d'adrénaline dans le plasma, occasionnées probablement par l'échantillonnage du sang. Chez l'homme, l'anesthésie au cyclopropane s'est accompagnée d'une augmentation importante du taux de catécholamine dans le plasma et, chez certains malades dont le P CO_2 était normal et chez d'autres dont le P CO_2 était élevé, d'une augmentation nette du taux de noradrénaline dans le plasma. Ces augmentations, lorsque le P CO_2 était normal, prenaient une valeur statistique appréciable, si on leur attribue comme cause, soit une anesthésie plus profonde, soit un effet de la chirurgie, soit les deux effets ensemble.

En ce qui concerne l'halothane, aussi bien chez les chiens que chez l'homme nous n'avons pas observé, au cours de l'anesthésie, d'augmentation importante du taux de catécholamine dans le plasma, bien que au cours de la chirurgie de surface chez l'homme anesthésié à l'halothane, nous avons trouvé une augmentation importante du taux d'adrénaline dans le plasma.

Les taux élevés de catécholamine dans le plasma, résultant de l'hémorragie durant l'anesthésie à l'éther, l'hypercarbie et l'asphyxie durant l'anesthésie au cyclopropane, l'hypercarbie durant l'anesthésie à l'éther chez des chiens surrénalectomisés, les études citées antérieurement, tout indique que les agents anesthésiques généraux n'exercent pas d'effets inhibiteurs marqués sur les réponses sympathicosurrénaliennes aux diverses formes de stimulation subies dans les salles d'opération.

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CIRCULATORY RESPONSE TO TILT WITH SOME ANTI-EMETIC AND SEDATIVE DRUGS*

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THE CIRCULATORY RESPONSE to tilt by normal healthy male subjects has been studied and compared in the large group of commonly used phenothiazine derivatives and with several narcotic analgesic drugs. With each of these drugs the dose selected for the study was within the therapeutic range of its most desirable action.[1,2] Several anti-emetics and sedative drugs are now being used or tested widely, although no specific comparative studies have been made of their effect on the human circulation. It was felt that such comparative data would be useful when selecting among the wide variety of premedicant drugs, and would also alert the anaesthetist when his patient was already receiving such medication for other reasons. The following report describes the comparative effect of the intravenous administration of trimethobenzamide, trimeprazine, diphenhydramine, dimenhydrinate, cyclizine, methaminodiazepoxide, and haloperidol on the pulse rate and blood pressure before and after 60° head-up tilt.

METHOD

Serial tests were done at intervals on eight healthy male subjects who were all between 20 and 30 years of age and weighed between 145 and 190 lb. The dose selected for each drug was within the optimum therapeutic range and was administered intravenously. The technique employed in studying these drugs was the same as reported previously.[1,2] Side-effects observed were annotated during and immediately after each experiment and every subject was requested to report on any discomfort or unusual symptoms during the 24–36 hours after each test.

RESULTS

The mean and standard deviation of the blood pressure and pulse rate at each time interval during each drug test was computed for the eight subjects and is shown in the Figures 1–7. Figure 8 shows the mean blood pressure and pulse rate during the periods in which the subjects were in the supine position and during 60° head-up tilt before and after each drug test.

All of the drugs caused a very slight decrease in the blood pressure shortly after administration without a consistent alternation in the pulse rate. The normal circulatory response to tilt was not impaired in the subjects after any

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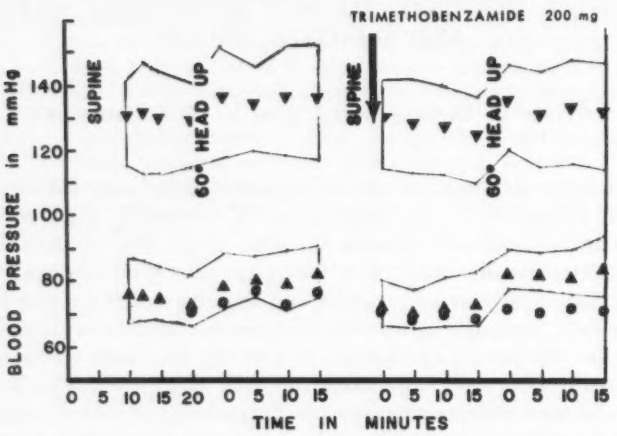

FIGURE 1. Blood pressure (systolic ▼, diastolic ▲) and pulse rate ● during test with trimethobenzamide 200 mg. (Tigan®). One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

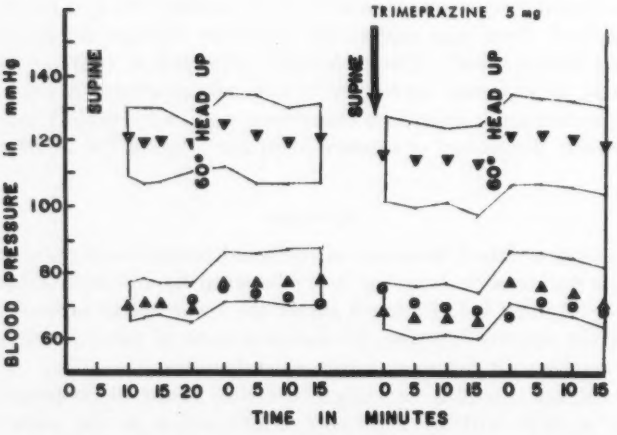

FIGURE 2. Blood pressure (systolic ▼, diastolic ▲) and pulse rate ● during test with trimeprazine 5 mg. (Panectyl®). One standard deviation for systolic and diastolic blood pressures is represented by solid lines.

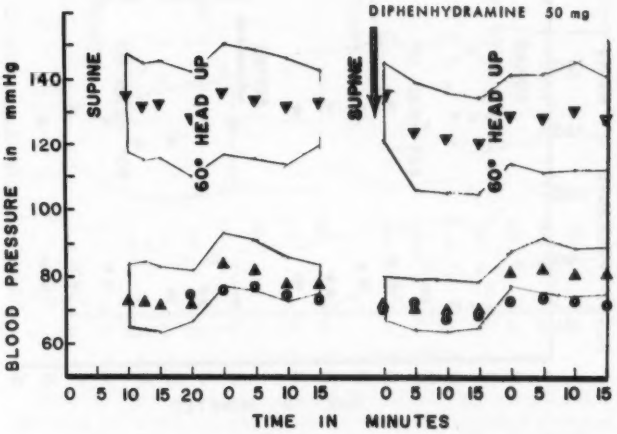

FIGURE 3. Blood pressure (systolic ▼, diastolic ▲) and pulse rate ● during test with diphenhydramine 50 mg. (Benadryl®). One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

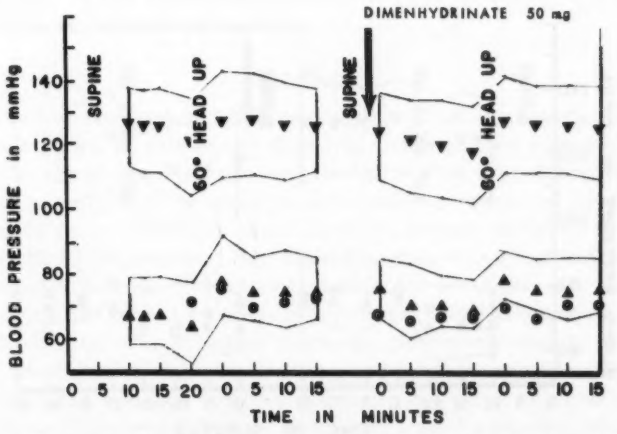

FIGURE 4. Blood pressure (systolic ▼, diastolic ▲) and pulse rate ● during test with dimenhydrinate 50 mg. (Gravol®, Dramamine®). One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

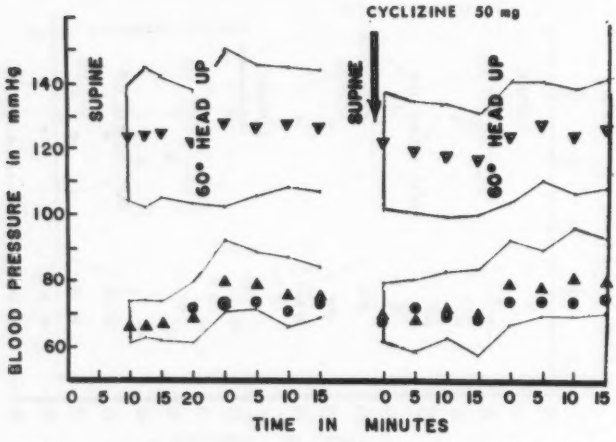

FIGURE 5. Blood pressure (systolic ▼, diastolic ▲) and pulse rate ● during test with cyclizine 50 mg. (Marzine®, Marezine®). One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

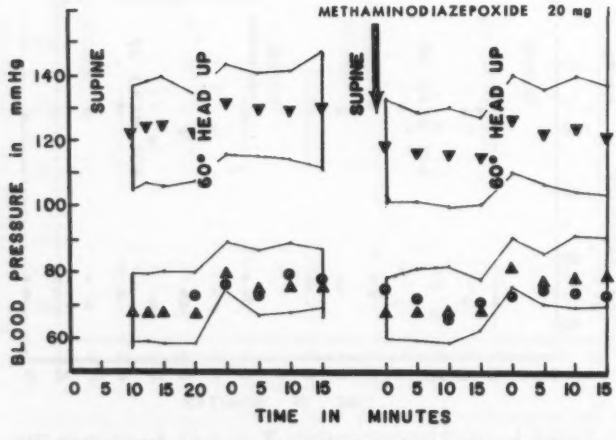

FIGURE 6. Blood pressure (systolic ▼, diastolic ▲) and pulse rate ● during test with methaminodiazepoxide 20 mg. (Librium®). One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

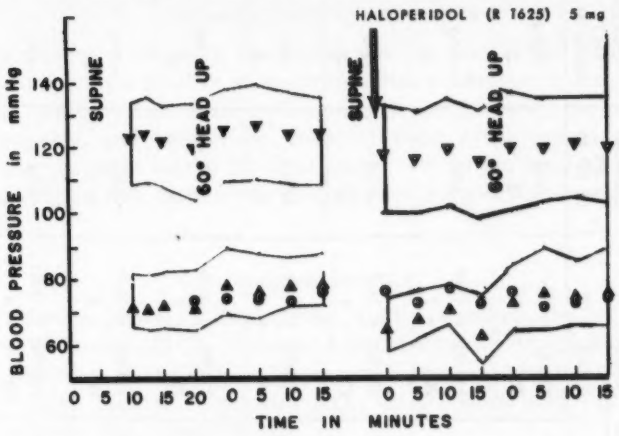

FIGURE 7. Blood pressure (systolic ▼, diastolic ▲) and pulse rate ● during test with haloperidol 5 mg. (R 1625). One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

of the drugs. Aside from varying degrees of drowsiness, which became apparent after each of the drugs except trimethobenzamide, no undesirable side-effects were observed, except with haloperidol which caused a variety of neuromuscular disturbances affecting the face and neck. This undesirable response to haloperidol usually did not appear for several hours and was delayed for almost 24 hours in three subjects.

DISCUSSION

There was less tendency to hypotension with a full therapeutic dose of each of the drugs tested in this report than was seen with the phenothiazine derivatives.[1] The circulatory response was similar to that seen during similar tests with narcotic analgesics.[2] In some of the subjects it appeared as if the drugs that produced more drowsiness also caused the greater tendency to a lowering of the systolic blood pressure, but when the data was examined closely, this was not in fact the case. Trimethobenzamide did not cause any subjective or objective effect, yet caused a similar change in the blood pressure and pulse rate to dimenhydrinate, which caused moderate drowsiness and a tired feeling. Similarly, trimeprazine, diphenhydramine, and cyclizine caused marked drowsiness and tiredness, and had virtually the same circulatory effect as methaminodiazepoxide and haloperidol, both of which only caused a pleasant relaxed feeling, without subjective drowsiness or tiredness. The antisialogogue effect of several of the above drugs were previously studied and the varying degrees of drowsy response were also observed for corresponding dosages, so that this effect is quite consistent.[3]

MEAN BLOOD PRESSURE & PULSE RATE IN SUPINE & 60° HEAD UP TILT BEFORE & AFTER ANTIEMETICS & SEDATIVES

DRUGS & DOSE	mgm.		BEFORE DRUG SUPINE (A)	BEFORE DRUG TILT (A)	AFTER DRUG SUPINE (B)	AFTER DRUG TILT (B)	CHANGE SUPINE (A TO B)	CHANGE TILT (A to B)
Trimethobenzamide	200	BP	128/74 ± 15/9	134/78 ± 16/8	125/72 ± 14/7	130/82 ± 14/7	-3/-2	-4/+4
TIGAN		P	70 ± 8	73 ± 7	68 ± 7	70 ± 8	-2	-3
Trimeprazine	5	BP	118/71 ± 10/6	120/78 ± 8/7	113/68 ± 13/8	119/76 ± 13/9	-5/-3	-1/-2
PANECTYL		P	71 ± 7	73 ± 7	70 ± 10	70 ± 7	-1	-3
Diphenhydramine	50	BP	130/74 ± 14/9	132/82 ± 16/8	124/72 ± 15/7	127/82 ± 14/7	-6/-2	-5/0
BENADRYL		P	74 ± 6	75 ± 8	71 ± 7	72 ± 9	-3	-3
Dimenhydrinate	50	BP	122/66 ± 13/11	124/75 ± 15/11	118/71 ± 15/9	123/75 ± 14/8	-4/+5	-1/0
GRAVOL;DRAMAMINE		P	70 ± 7	71 ± 8	65 ± 7	68 ± 7	-5	-3
Cyclizine	50	BP	122/68 ± 19/7	126/78 ± 20/9	117/70 ± 17/11	123/80 ± 16/8	-5/+2	-3/+2
MARZINE; MAREZINE		P	71 ± 8	72 ± 8	69 ± 7	73 ± 7	-2	+1
Methaminodiazepoxide	20	BP	122/69 ± 15/11	129/78 ± 14/9	115/69 ± 14/10	124/80 ± 16/9	-7/0	-5/+2
LIBRIUM		P	73 ± 7	76 ± 9	74 ± 9	74 ± 8	+1	-2
Haloperidol	5	BP	120/73 ± 13/8	123/79 ± 14/9	114/69 ± 16/8	117/74 ± 17/11	-6/-4	-6/-5
R 1625		P	73 ± 9	74 ± 12	73 ± 10	72 ± 9	0	-2

FIGURE 8

Summary and Conclusions

The circulatory response in the supine position and in the 60° head-up tilt was compared in eight healthy male subjects with a therapeutic dose of trimethobenzamide, trimeprazine, diphenhydramine, dimenhydrinate, cyclizine, methaminodiazepoxide, and haloperidol. None of these drugs caused a significant alteration in the pulse rate or blood pressure, even in the head-up tilt position. Aside from drowsiness, none of the drugs except haloperidol caused undesirable side-effects.

Acknowledgment

The following pharmaceutical firms kindly supplied drugs for testing: Burroughs-Wellcome and Co. (Canada) Ltd., Montreal, P.Q.; Hoffman LaRoche Limited, Montreal, P.Q.; F. W. Horner and Company, Montreal, P.Q. (grant-in-aid); Poulenc Limited, Montreal, P.Q.; G. D. Searle and Co. of Canada, Ltd., Brampton, Ont. (grant-in-aid).

Résumé

Nous avons comparé chez huit sujets mâles en santé, la réponse circulatoire à une élévation de la tête de 60°, après une dose thérapeutique de triméthobenzamide, de triméprazine, de diphenhydramide, de cyclizine, de méthaminodiazepoxide et de halopéridol. Aucun de ces médicaments n'a causé de changement important de la vitesse du pouls ou de la tension artérielle. Si l'on excepte les étourdissements, aucun de ces médicaments, à part l'halopéridol, n'a causé d'effets secondaires indésirables.

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LES DOSES DE SUCCINYLCHOLINE EMPLOYÉES EN ANESTHÉSIE SONT-ELLES TROP ÉLEVÉES?*

GASTON COMTOIS, M.D.,† EMILE BERTHO, M.D., F.R.C.S.(C.),‡ AND ALEXANDRE TARDIF, M.D.§

DANS LE LABORATOIRE de chirurgie expérimentale où la succinylcholine est très employée, spécialement pour prélever du sang chez les chiens, nous sommes impressionnés chaque jour par les doses minimes et efficaces de cette drogue comparées aux doses élevées employées en chirurgie humaine. Nous sommes également surpris de constater, dans les salles de réveil, la cyanose, parfois légère mais existante, des extrémités chez les opérés, et cette cyanose peut se prolonger une demi-heure et parfois même une heure. Nous sommes convaincus que la succinylcholine, ou les curarisants en sont responsables pour une large part. Il existe évidemment d'autres médicaments à action dépressive sur les centres respiratoires (barbituriques, narcotiques, etc.) mais l'action prolongée[1] de la succinylcholine sur les muscles de la respiration aboutit à une ventilation imparfaite; et cette action est d'autant plus prolongée que l'état de l'opéré est détérioré et que des doses répétées de succinylcholine ont été employées.

Il faut même aller plus loin, c'est-à-dire incriminer la succinylcholine de certaines complications pulmonaires, atélectasie, broncho-pneumonie, etc., surtout chez les gens âgés.

Après un bref historique sur la succinylcholine, sur sa constitution chimique, sur son mode d'action ainsi que sur son sort dans l'organisme, seront exposées les méthodes expérimentales employées, ainsi que les résultats obtenus.

HISTORIQUE

Dès 1906, Hunt et Traveau[2] avaient employé la succinylcholine chez les animaux de laboratoire. Ils n'avaient cependant pas parlé de son activité de bloquage neuro-musculaire. Cette propriété de la succinylcholine est demeurée inconnue pendant plus de 40 ans. Ce n'est qu'en 1949 que l'action curarisante de la drogue fut décrite indépendamment par les Italiens, les Anglais et les Américains. Bovet et ses collaborateurs décrivaient en 1949 les propriétés de la succinylcholine et publiaient en 1951[3] leurs recherches sur les poisons curarisants de synthèse. Philipps, publiait également en 1949 un travail sur les substituts synthétiques du curare.[4] Ces deux chercheurs, tentaient de démontrer l'action

*Travail présenté au congrès des anesthésistes de la Province de Québec tenu à l'Hôtel-Dieu St-Vallier de Chicoutimi le 28 mai 1960, et effectué grâce à la collaboration des autorités administratives de l'Hôtel-Dieu St-Vallier de Chicoutimi.

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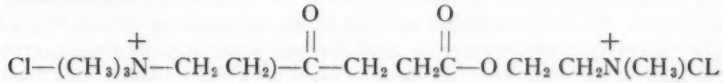
du "bloquage myoneural" de cette drogue. En 1951, Low et Tammelin[5] mirent au point une nouvelle technique pour préparer la succinylcholine sous forme de poudre cristalline exempte d'impureté.

CHIMIE ET MODE D'ACTION[1,6,13]

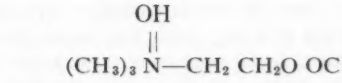
La succinylcholine, qui semble à première veu un "paradoxe pharmacologique," a une structure chimique correspondant à une double acétylcholine.

Formule

Succinylcholine:



Acetylcholine:



De plus, dans sa structure, nous remarquons plusieurs détails communs à un grand nombre de relaxants musculaires. La molécule contient deux atomes de nitrogène quaternaire, ou groupes onium, placés à distance l'un de l'autre. Ces groupes onium sont suffisamment basiques pour former un sel avec un acide fort. Ce sel réagit ensuite avec l'eau pour donner des solutions acides.

Cependant la succinylcholine diffère de bien d'autres relaxants musculaires par cette propriété qu'elle a de s'hydroliser. Ceci serait dû à la présence de deux groupes esther dans sa chaîne et expliquerait sa brièveté d'action *brièveté relative.*

L'effet principal de la succinylcholine est l'inhibition[7,8] de la transmission neuro-musculaire. Cette action diffère de celle du curarisant *vrai.* Ce dernier augmente le seuil d'excitabilité de la plaque myoneurale tout en abaissant le degré d'efficacité déplorisante de l'acétylcholine. Ceci explique pourquoi les antagonistes de la cholinestérase (prostigmine, néostigmine) sont des antidotes aux curarisants vrais, et non à la succinylcholine.

L'administration de succinylcholine entraine un bloquage neuro-musculaire semblable à l'injection d'une haute dose d'acétylcholine. Cette action est dûe à son aptitude intrinsèque d'effet dépolarisant sur la plaque myoneurale et sur les fibres musculaires environnantes. La cholinestérase ne la détruisant pas, l'effet de dépolarisation se prolonge. Les anticholinestérases n'ont par conséquent aucune action.

Les muscles sont paralysés dans l'ordre suivant: les muscles de l'œil, de la face et du cou d'abord, les muscles des membres ensuite, puis ceux de l'abdomen et des intercostaux et enfin le diaphragme.

La succinylcholine n'est pas détruite par la cholinestérase[9,10] proprement dite. Bien plus, les anticholinestérases prolongent l'action de la succinylcholine et sont donc absolument contre-indiquées, car elles détruisent aussi la pseudo-cholinestérase responsable elle-même de la destruction de la succinylcholine. Cette destruction est faite en deux temps:

(*a*) Formation de succinylmonocholine et de choline. La première aurait une action plus prolongée que sa parente qui est la succinyldicholine.

(*b*) Formation de choline et d'acide succinique, constituants normaux du plasma.

Méthodes employées

Dans le laboratoire de chirurgie expérimentale, 82 chiens ont été utilisés pour prélèvements de sang au cours des circulations extra-corporéales. Tous ces chiens étaient des bâtards. Leur poids variait de cinquante à cent vingt livres; et l'âge, de deux à quinze ans. Un diachylon autour de la gueule constituait la seule prémédication. Aucune anesthésie n'a été faite, car ce sang devait être exempt de toute substance anesthésique ou analgésique. Aussi la seule drogue employée a été la succinylcholine. Une seringue à insuline a été utilisée pour l'injector. La ponction veineuse a été faite dans la veine tibiale antérieure après rasage du poil et désinfection locale. Les doses de succinylcholine ont varié de 6 à 8 mg.; 6 mg. pour les chiens plus petits et 8 mg. pour les chiens plus gros. Le produit employé avait une concentration de 10 pour cent, c'est-à-dire 20 mg. au c.c. En moyenne 10 secondes après l'injection de la succinylcholine, les paupières du chien se ferment et apparait une trémulation des muscles du front et du cou, suivie de la chute du chien; puis les sphincters se relâchent et le chien devient absolument flasque vingt-cinq secondes en moyenne après le début de l'injection de la succinylcholine. L'intubation endo-trachéale est faite dans les trente à soixante secondes qui suivent l'injection et la ventilation contrôlée est pratiquée. Le diaphragme, dernier muscle à se paralyser, s'arrête 40 à 60 sscondes après l'injection. La durée d'action de ces doses de succinylcholine a été de 15 à 20 minutes, avec une moyenne de 16 minutes.

Les doses de succinylcholine ont été réduites à 6 mg. puis à 4 mg. toujours en utilisant une seringue à insuline. Mêmes constatations que plus haut et même durée d'action. D'autre part, plus l'animal est âgé, plus la durée d'action est prolongée.

Chez tous ces chiens qui n'avaient reçu aucune prémédication, les constations suivantes ont été enregistrées après injection de succinylcholine:

(*a*) Un ralentissement marqué des battements cardiaques allant jusqu'à 20 à la minute. Normalement le cœur du chien bat de 80 à 120 à la minute. Ce phénomène a cédé spontanément 2 à 3 minutes plus tard à la suite de la ventilation contrôlée.

(*b*) Une arythmie qui a cédé en même temps que la bradycardie.

(*c*) Une sécrétion salivaire excessivement abondante dans tous les cas.

La moitié des chiens ont été gardés en vie pour être utilisés à nouveau comme donneurs de sang. Par exemple un chien pesant 126 lb. a été saigné 4 fois. La première fois il a reçu 8 mg. de succinylcholine, c'est-à-dire 0.06 mg. environ par livre de poids. Les constatations énumérées plus haut ont été observées. A la deuxième et à la troisième intervention cet animal a reçu 6 mg. et 4 mg. de succinylcholine, mêmes constatations. A la quatrième et dernière saignée, 3 mg. de succinylcholine seulement ont été injectés, c'est-à-dire 0.024 mg. par livre de poids. Les constatations et les résultats obtenus furent exactement les mêmes.

Ces chiens ont été saignés tous les mois environ, laps de temps nécessaire pour refaire une formule sanguine normale.

Dans un deuxième groupe d'expériences, l'étude de doses répétées de succinylcholine a été faite. Quatre chiens font l'objet de cette étude.

Avant de commencer l'expérience proprement dite, avec la succinylcholine l'installation suivante a été faite sur chaque chien:

(*a*) Ponction de la veine tibiale antérieure à l'aide d'une aiguille reliée à un "stopcock" (appareil qui permet d'injecter mais n'autorise pas le retour sanguin).

(*b*) Anesthésie du chien au penthotal et intubation endotrachéale mais l'animal doit respirer spontanément. (En moyenne 150 mg. d'une solution de penthotal à 2½ pour cent a été suffisante dans tous les cas.)

(*c*) Désinfection de la région fémorale au zéphiran. Dissection de l'artère fémorale et mise en place d'un tube de polyéthylène dans cette artère. Ce tube de polyéthylène est relié à un appareil à Hg et à un "Transducer" pour enregistrer la pression d'une façon continue.

(*d*) Installation de l'électrocardiographe et de l'électroencéphalographe. Pour avoir un tracé électrocardiographique identique à celui de l'humain, les électrodes sont inversées au niveau des pattes antérieures.

(*e*) Au cours de l'expérience, le chien sera relié au moyen du tube endotrachéal à un respirateur automatique fonctionnant sous air comprimé.

Après tous ces préparatifs, la succinylcholine sera injectée à l'aide d'une seringue à insuline. La période d'apnée sera le laps de temps qui s'écoule entre l'heure de l'arrêt de la respiration après l'injection de la succinylcholine et l'heure où le chien se ventilera spontanément sans aucune cyanose: la langue est le témoin le plus fidéle.

Chien no 71

Ce chien de 34 lb. a reçu comme prémédication: morphine 1/6 de gr. et atropine 1/150 de gr. Une première dose de 3 mg. de succinylcholine est injectée; 10 secondes plus tard la respiration s'arrête et ne reprend de façon satisfaisante qu'après 12 minutes. Une deuxième injection de 3 mg. entraîne une période d'apnée de 13 minutes et une troisième injection de 3 mg., une apnée de 24 minutes. Pendant tout ce temps, le chien bave abondamment malgré la prémédication.

Chien no 28

Ce chien de 40 lb. a reçu, une heure avant l'expérience, morphine 1/6 gr. et atropine 1/150 gr. Puis 4 mg. de succinycholine sont injectés rapidement par voie i.v. La période d'apnée est de 20 minutes. Une deuxième dose de 4 mg. est injectée et 30 minutes plus tard, la respiration spontanée n'est pas encore apparue. A ce moment 5 mg. de prostigmine sont injectés. L'electrocardiogramme montre des altérations cardiaques: ralentissement du cœur avec arythmie et troubles de la conduction. La T.A. cependant demeure normale. Si le respirateur est débranché du tube endotrachéal, la T.A. monte graduellement et le cœur devient de plus en plus irrégulier: effets dûs à l'anoxie. La douleur (par exemple, la torsion des orteils) provoque également une élévation de la T.A. et une accélération du

pouls. Donc la succinylcholine n'enlève pas la douleur. La salivation est également abondante malgré la prémédication. Une troisième dose de 8 mg. est injectée et il faut attendre 60 minutes pour obtenir une respiration spontanée, qui ici cependant, ne se fait qu'aux dépens du diaphragme. Le chien est extubé. La T.A. monte graduellement, le pouls devient de plus en plus irrégulier et l'animal meurt dans les minutes qui suivent.

Chien no 13

Ce chien de 26 lb. ne reçoit aucune prémédication. Une première dose de succinylcholine de 3 mg. est administrée, elle entraîne une période d'apnée de 15 minutes. L'attention est d'abord portée sur la nature des preimers mouvements respiratoires. Ceux-ci débutent au diaphragme. L'hypersalivation est toujours enregistrée. Une deuxième injection de 3 mg. entraîne une apnée de 20 minutes. Cette apnée dure 35 minutes après l'administration de 6 mg. de succinylcholine, 60 minutes après l'injection de 12 mg. La respiration ne se fait qu'aux dépens du diaphragme et la cyanose de la langue apparait dès que le respirateur est débranché. Le chien est quand même désintubé mais il se cyanose de plus en plus et meurt au bout de quelques minutes noyé dans ses sécrétions.

Chien no 60

Ce chien pesant 28½ lb. ne reçoit aucune prémédication; 4 mg. de succinylcholine sont d'abord injectés. La T.A. monte brusquement de 140 mm. de Hg à 160 mm. de Hg pour s'abaisser en 30 secondes et redevenir normale en 60 secondes. Le tracé E.C.G. n'est aucunement modifié mais la période d'apnée dure 15 minutes. Puis 8 mg. de succinylcholine sont injectés. La T.A. monte brusquement jusqu'à 180 mm. de Hg. Le cœur reste régulier, 20 minutes après cette troisième dose le chien ne respire pas encore. Après une quatrième dose de 30 mg., même poussée de la T.A. Celle-ci fait un bond à 200 mm. de Hg pour redescendre ensuite graduellement. Le cœur fait quelques petites pauses. Les pupilles sont extrêmement dilatées; il n'existe aucun réflexe. Il faudra attendre 3 heures pour obtenir une respiration spontanée satisfaisante et désintuber le chien.

Discussion

S'il est admis que tout le règne animal* réagit de façon identique à l'administration d'une drogue (l'homme est un animal) il est possible de tirer les conclusions suivantes et d'en discuter:

(*a*) Les doses de succinylcholine efficaces sont peu élevées, dans l'ordre de 0.05 mg. à 0.07 mg. par livre de poids dans le laboratoire; alors que, actuellement dans la pratique courante de l'anesthésie, la succinylcholine se donne à la dose de 0.3 mg. à 0.5 mg. et même davantage par livre de poids chez un même individu au cours d'une même anesthésie.

Couramment, dans la littérature, il est dit que la dose de succinylcholine efficace varie de 40 à 80 mg. chez l'être humain adulte suivant son poids. Cela

*Pour démontrer cette assertion il faudrait faire des études chimiques plus poussées, en particulier doser la cholestérinase et la pseudo-cholestérinase dans le sang du chien et comparer les dosages à ceux rencontrés chez l'homme.

veut dire que si la dose moyenne est de 50 mg. un individu de 160 lb. recevra 0.3 mg. par livre de poids; cette dose est beaucoup supérieure à la dose efficace trouvée au laboratoire.

A l'Hôtel-Dieu St-Vallier de Chicoutimi, les doses de succinylcholine employées pour intuber les malades ont été réduites sensiblement. Actuellement avec 20 mg. et même 15 mg., il est possible d'intuber tout adulte à condition d'y mettre un peu de dextérité et de rapidité.

(*b*) La durée d'action pour une première dose de succinylcholine est de 12 à 20 minutes. Plus cette dose est répétée plus la période d'apnée se prolonge. Il y a donc un effet cumulatif. Cela nous amène à douter de l'absence de danger du goutte à goutte intra-veineux[8] et surtout de l'absence de danger de l'administration de la succinylcholine par voie intra-musculaire.[11] En effet l'administration intra-musculaire peut échapper à tout contrôle d'absorption et partant de destruction. Si pour une raison quelconque l'absorption est retardée, le malade retourne à la salle de réveil, voire même à sa chambre d'hôpital accusant une ventilation pulmonaire nettement insuffisante. Ce qui engendre la cyanose, l'atélectasie pulmonaire voire la broncho-pneumonie chez certains opérés en particulier âgés. L'effet primordial de la succinylcholine, en effet, est de paralyser les muscles respiratoires. D'autres facteurs évidemment entrent en cause pour expliquer la dépression respiratoire au cours de la période postopératoire, tels: la prémédication, l'anesthésie, le choc opératoire—mais la succinylcholine a un effet prépondérant.

(*c*) La succinylcholine engendre l'hypersalivation, autre obstacle très important à la ventilation pulmonaire pour un individu qui arrive de la salle d'opération.

(*d*) L'administration de prostigmine[1] ne neutralise en rien l'effet de la succinylcholine. Au contraire, elle semble en prolonger l'action.

(*e*) L'administration de succinylcholine à faible dose n'a peu ou pas d'effet sur la tension artérielle ni sur le rythme cardiaque. A haute dose cependant la succinylcholine augmente la T.A. et entraine des modifications de la conduction intra-cardiaque.

A la lumière des quelques données résumées au début, à la lumière aussi des constatations et des résultats enregistrés au laboratoire, il est très probable que les doses de succinylcholine employées à la salle d'opération sont trop élevées. L'anesthésie se fait habituellement sur des malades où les facteurs suivants peuvent influencer la durée d'action de la succinylcholine[7]:

(*a*) Il peut y avoir un taux insuffisant de pseudocholinestérase dans le sang. Normalement le taux de cette enzyme est présent dans les proportions de 65 à 110 unités au c.c. Elle est détruite par la prostigmine, tout comme la cholinestérase. Le taux de pseudocholinestérase est beaucoup plus élevé chez l'enfant que chez l'adulte et est très bas chez le vieillard. D'autre part un taux abaissé de pseudocholinestérase est retrouvé dans les cas suivants: après radiations thérapeutiques; après contaminations par substances phosphorées dues aux insecticides; dans les états d'hyperpyrexie; au cours des insuffisances cardiaques; au cours des états urémiques; dans les maladies du foie; au cours des maladies de dénutrition; dans les anémies sévères; dans l'hyperthyroidisme; chez tout grand malade.

(*b*) Il peut y avoir destruction incomplète de la succinylcholine. Il a été dit plus haut que la succinylmonocholine, produit intermédiaire, avait une action plus prolongée que sa parente la succinyldicholine. De plus la choline elle-même quand elle est présente en excès, aurait une action de bloquage sur la plaque myoneurale; excès qui pourrait être dû à l'administration de trop fortes doses.

(*c*) Il peut y avoir acapnie ou hypercapnie dues à l'hyper ou l'hypoventilation assistée ou contrôlée au cours de l'apnée créée par la succinylcholine, empêchant ainsi l'action normale du centre bulbaire respiratoire.

(*d*) Il peut y avoir chambardement du réflexe de Hering-Breuer dû à la distension en plus ou en moins des alvéoles pulmonaires au cours de la respiration contrôlée ou assistée.

(*e*) Il peut y avoir hyper ou hypocalcémie.[13]

(*f*) Il peut y avoir association de drogues: barbituriques-opiacés qui dépriment le centre respiratoire.

(*g*) Il peut y avoir inactivation de la pseudocholinestérase par la sérotine.[4]

Résumé et conclusion

Les doses de succinylcholine employées en anesthésie actuellement seraient, à notre avis, trop élevées et certaines complications pulmonaires post-opératoires seraient attribuables à cette drogue (atélectasie, broncho-pneumonie etc.).

Après avoir donné un brief résumé sur l'historique de la succinylcholine, sur sa constitution chimique sur son mode d'action ainsi que sur son sort dans l'organisme, les résultats obtenus dans le laboratoire sont exposés.

Dans une première série d'expérience, 82 chiens ont été utilisés comme donneur de sang au cours de circulations extra-corporéales. Chez ces 82 chiens, la dose efficace de succinylcholine administrée a varié de 0.024 mg. à 0.06 mg. par livre de poids. Dans une deuxième série d'expériences, 4 chiens ont fait l'objet d'une étude plus complète; les conclusions ont été les suivantes:

(*a*) La dose de succinylcholine efficace varie de 0.03 à 0.07 mg. par livre de poids dans le laboratoire.

(*b*) La succinylcholine administrée à doses répétées a un effet cumulatif.

(*c*) La succinylcholine engendre l'hypersalivation en dépit de la prémédication.

(*d*) La succinylcholine à hautes doses a un effet hypertensif malgré la prémédication et malgré l'anesthésie au penthotal.

(*e*) La prostigmine a un effet nocif en présence de la succinylcholine.

Dans le service d'anesthésie de l'Hôtel-Dieu St-Vallier de Chicoutimi, les doses de succinylcholine administrées aux malades ont été sensiblement réduites tout en conservant les mêmes résultat.

Reconnaissance

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COMPARATIVE EFFECT OF CURARE AND SUCCINYLCHOLINE ON SURVIVAL TIME OF SHOCKED RATS*

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A PATIENT who had been severely traumatized in an automobile accident needed anaesthesia for an exploratory laparotomy. It was believed that her spleen had been ruptured. She was put to sleep with a few breaths of cyclopropane, and 40 mg. of succinylcholine were given intravenously. Within a few seconds she went into circulatory collapse. In spite of infusion of blood under pressure into three different veins simultaneously, she expired. She was found to have a ruptured liver as well as a ruptured spleen. Because of the sudden circulatory collapse on administration of succinylcholine, the question arose as to whether the collapse might have been enhanced by the relaxing agent. The possibility was mentioned that curare might have been better.

Accordingly, experiments were carried out to determine the effect of each of these relaxing agents under conditions of shock.

METHOD

Wistar strain female white rats weighing between 190 and 210 gm. were shocked according to the method of Smith, Williams, Blood, and D'Amour.[1] Briefly, this entails anaesthetizing the animals with pentobarbital, cannulating the trachea to ensure a patent airway, and pinching the cecum of the rats 3 times per sec. for 15 min. with a standardized pressure. One hundred per cent of the animals die, and the time of survival is a measure of the resistance of the rat to the stress.

A control group included 30 animals who were given 0.4 c.c. of normal saline intravenously to equalize fluid injections.

A second group of control animals was anaesthetized, shocked, and given 0.4 c.c. of normal saline intravenously. They were then given artificial respiration with oxygen using a "windshield wiper" respirator. Survival time was noted.

A third group of animals was given succinylcholine 1.0 mg./kg. intravenously after the shocking procedure. Artificial respiration was utilized.

The fourth group of animals was treated the same as the third except that d-tubocurarine 0.3 mg./kg. was administered in place of the succinylcholine given the third group.

RESULTS

Table I shows that there was no significant difference in survival times of the

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TABLE I

COMPARATIVE EFFECT OF CURARE AND SUCCINYLCHOLINE ON SURVIVAL TIME OF SHOCKED RATS

No. of rats	Procedure after shock		Average survival time (min.)
30	Normal saline	Spontaneous respiration	175 A
20	Normal saline	Artificial respiration	200 B
24	Succinylcholine	Artificial respiration	216 C
10	Curare	Artificial respiration	178 D

A–B, not significant; A–D, not significant; B–C, not significant; B–D, not significant; C–D, not significant; A–C, $p = 0.01$.

control as compared to either group of rats which had had relaxing agents. Neither was there a significant difference between the two groups of experimental animals although the animals receiving curare had a somewhat shorter average time of survival. The only statistical significant value occurred with a shorter survival of animals who had no artificial respiration compared to those who had succinylcholine and artificial respiration ($p - 0.01$.).

DISCUSSION

Most evidence presented to date indicates that administration of succinylcholine is followed by a transient rise of blood pressure.[2] This information has come from healthy patients and animals. It would not be inconceivable that results using shocked subjects might afford different responses. The rat seemed to be a good subject because its response to a definite dose of succinylcholine is quite similar to, and its average concentration of cholinesterase is reported to be somewhat higher than, that of a human being.[3]

Clinical doses of curare do not have untoward effects on the circulatory system, although large doses are known to be ganglionic blocking agents. If animals are not healthy, it is again not inconceivable that relatively small doses might produce untoward effects.

Data obtained in these experiments reveal no definite choice of relaxing agent to be used in cases of shock. Since there was no significant difference in survival time of controls as compared to the animals receiving relaxant drugs, one has no evidence from this work that the circulatory collapse of the patient whose demise stimulated these experiments was enhanced by the choice of relaxing agent.

SUMMARY

Rats were shocked by pinching the cecum, a method which produces 100 per cent mortality. Time of survival using artificial respiration was noted. Another group of animals was treated similarly, except that succinylcholine was administered immediately following the shocking procedure. Still another group was studied using curare rather than succinylcholine. No statistically significant differences in survival time were found between any of the three groups.

RÉSUMÉ

Un malade traumatisé a été soumis à l'anesthésie avec une dose minima de cyclopropane, et on lui a administré de la succinylcholine. Quelques secondes après l'administration de ce succinylcholine, il est apparu un collapse circulatoire. La question s'est posée: chez un malade en état de choc, serait-il préférable de donner du curare ou de la succinylcholine.

C'est dans le but d'obtenir des renseignements sur ce sujet que nous avons fait des recherches.

On a employé comme témoins des rats, anesthésiés au nembutal, chez qui on provoquait un état de choc en leur faisant subir un traumatisme intestinal, ce qui entraînait la mort dans un temps limité. A un second groupe de rats traités de la même façon, on a administré par voie endoveineuse, aussitôt le choc installé, de la succinylcholine à raison de l. mg./kg. A un troisième groupe traité comme le premier, l'on a donné par voie endovieneuse, aussitôt le choc installé, du curare à raison de 3 mg. par kilo. On n'a pas noté de différence appréciable dans le temps de survie entre les animaux qui ont reçu de la succinylcholine et ceux qui ont reçu du curare.

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NEUROLOGICAL COMPLICATIONS OF SPINAL ANAESTHESIA

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THIS STUDY reports more than 20,000 consecutive spinal anaesthetics administered at the Veterans' Administration Hospital, Hines, Illinois, during the years 1948 to 1959, inclusive. In addition to the 20,000 cases analysed herein, approximately another 10,000 spinal anaesthetics were administered by the members of the staff of this hospital at other institutions (University of Illinois Research and Educational Hospitals and the Veterans' Administration West Side Hospital, Chicago) during the years mentioned. These have not been individually analysed (as are the cases in this paper), but a screening analysis has shown findings approximately the same in these 10,000 cases and certainly comparable to those in the 20,000 reported.

In analysing these cases, neurological complications were sought and the following types were looked for particularly:

Cerebrovascular accident within 10 days of spinal anaesthetic; transverse myelitis (para- or quadriplegia); peripheral nerve lesion; foot drop; persistent headache (longer than one week); neuritides; paralyses; muscular weakness; arachnoiditis, meningitis, meningismus; nerve deafness; strabismus or other cranial nerve lesions; herniated intervertebral disc; persistent lower bowel and bladder dysfunction; cauda-equina syndrome; chronic backache; any other neurological complications not listed here.

At this point, it should be emphasized that while these 17 categories were sought, not all of them were found in the cases studied.

The administration of these anaesthetics was, in a large part, performed by the resident staff in anaesthesiology, although residents in surgery, who were assigned to the anaesthesiology section, attending anaesthesiologists, consultants, and so on, performed a number of them.

The method of study of the 20,000 cases consisted in examining the operative notes and discharge summaries of all patients who were given spinal anaesthesia during the years listed. All records of subsequent admission of these same patients up to the present time were examined, and in every case in which a neurological diagnosis had been made, the entire chart of the patient was carefully gone over by several members of this team.

Of the 20,000 cases, approximately 1,300 charts were reviewed in detail,

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since these were the only patients carrying any neurological diagnoses. Upon review of these 1,300 charts, it was found that the neurological diagnoses in all but 34 instances were obviously not due to *sequelae* of spinal anaesthesia. The remainder of the cases were ruled out as being complications on the basis of one or more of the following reasons:

1. The neurological disease existed prior to the administration of spinal anaesthesia and was unchanged thereby.
2. The neurological disorder was obviously due to causes other than spinal anaesthesia, such as trauma.
3. Death, when it occurred, had no connection with anaesthesia.
4. Death was due to complications other than a neurological disorder.
5. The only complication was post-spinal headache of less than seven days' duration. (This length of time for a post-spinal headache was an arbitrary choice on our part, since we felt that while post-spinal headaches are certainly a neurological complication of spinal anaesthesia, we were more interested in permanent or semi-permanent *sequelae* than in the temporary self-limiting ones. This will be discussed more fully later in the paper.)

Of the 34 remaining cases in the study, after closer screening and perusal of the entire charts of these patients, 10 were found to have no real causal connection with the administration of spinal anaesthesia, although in several instances, first glance would lead one to believe that they had been due to spinal anaesthesia. When the 10 cases were carefully analysed, it was found that either they existed prior to anaesthesia and were not aggravated thereby, or that they were completely unrelated to anaesthesia. These ten are probably the most important of the entire group of cases. They are representative of the type of *sequelae* which are so often blamed on spinal anaesthesia both by laymen and professional people. In truth, the administration of spinal anaesthesia probably was a purely incidental thing and had nothing to do with the patient's neurological condition; yet it is cases of exactly this nature which are frequently the subjects of malpractice lawsuits. These cases will be discussed individually.

Case 1

A 50-year-old male had an established diagnosis of demyelinization of the spinal cord and peripheral nerves on a vitamin B deficiency basis. Three days later before the report was in the patient's chart, he was given continuous spinal anaesthetic for biliary tract exploration. Postoperative course was completely uneventful. Had he suffered further progress in his disease, it would have been difficult to disprove the effect of the anaesthesia in aggravating it. The choice of spinal anaesthesia in cases of this kind is condemned because it is probable that the disease will progress and also that the anaesthetic agent may actually do harm.

Case 2

The patient was given a spinal anaesthetic for repair of right inguinal hernia. At that time, serology was not recorded in the chart. He was readmitted 18 months later with an apparent cerebrovascular accident. Examination revealed luetic taboparesis. This was not an anaesthetic complication, but it emphasizes the importance of careful pre-anaesthetic study of all patients, since any exacerbation of his condition might readily have been blamed on the anaesthesia. Here again, in retrospect, the choice of anaesthetic was a poor one. Any progress of the disease could be blamed on the anaesthetic agent.

Case 3

The patient was readmitted for treatment of weakness of the legs. He gave a history of "weakness of the legs" for six months prior to hospitalization. Shortly before the onset of weakness, he had a bilateral saphenous ligation and vein stripping under spinal anaesthesia. However, when the chart of the previous admission was closely scrutinized, the complaint of "weakness in legs" was revealed in the initial history prior to administration of the spinal. Neurological examination on the day prior to operation resulted in a diagnosed "quadriceps weakness, disuse" and cleared him for operation. It was an error of judgment to have given this patient a spinal anaesthetic since any aggravation may conceivably have been blamed on anaesthesia.

Case 4

A 50-year-old male had a repair of an inguinal hernia under spinal anaesthesia. He was discharged after an uneventful postoperative course. He was readmitted one month later with a history of having had a convulsion while unloading a truck that afternoon. There was confusion as to whether he convulsed then fell and struck his head, or whether he fell, struck his head, and then had a convulsion. The patient had a generalized epileptiform seizure while in the hospital admitting room. A diagnosis of post-traumatic epilepsy was made. He had no further episodes during his stay in the hospital.

This case is difficult to analyse because of paucity of information. Since no witnesses were present at the time of his injury, one cannot say whether there was any basis at all for assuming that this was anything more than concussion with subsequent epileptiform attack. Assuming that the seizure occurred prior to the injury, it is still rather difficult to connect this with an uncomplicated spinal anaesthesia more than a month previously and with no symptoms during the intervening time.

Case 5

A 36-year-old male had a gastric resection for duodenal ulcer under continuous spinal anaesthesia. He made an uneventful recovery. Eighteen months later, he was readmitted with complaints of dizziness, difficulty in walking, and weakness of the left leg for one year. He had loss of sexual power for nine months. There was no blurring of vision. He was diagnosed as having multiple sclerosis. This was confirmed on subsequent admissions. Had the neurological work-up been less careful, this could easily have been blamed on the anaesthesia.

Case 6

A 50-year-old male underwent a cholecystectomy and appendectomy in July 1953 under continuous spinal anaesthesia with 4 per cent procaine. Postoperatively, the patient failed to regain use of his legs. Laminectomy was performed two days later, at which time a tumour was found to be compressing the spinal cord. Biopsy of the tumour was made and diagnosed as Hodgkin's disease. This diagnosis had been unsuspected, but a few days subsequently, a record of a former admission which had been misfiled was found, and it was noted that in December, 1952, eight months previously, this diagnosis had been made on lymph node biposy. The patient remained paraplegic and expired in May, 1954, in spite of therapy for Hodgkin's disease.

The spinal anaesthesia may have precipitated an earlier onset of paraplegia in this patient, but from the size of the spinal tumour the end result was inevitable whether or not it had been done. It is regrettable that the information as to the patient's diagnosis was not made available prior to surgical intervention, but even in the best regulated teaching institutions this can occasionally occur.

Case 7

A 36-year-old male underwent hemorrhoidectomy under spinal anaesthesia in April 1955. He was discharged asymptomatic one week later. Five months later, in October 1955, he was readmitted with complaints of "blackout episodes." Work-up at this time resulted in a diagnosis of grand mal epilepsy, probably secondary to a space-occupying lesion of the

left fronto-parietal region. The patient is still being followed as a brain tumour suspect. Surgery was not performed as the lesion could not be demonstrated either by means of carotid or vertebral angiograms or pneumoencephalogram.

While it is possible theoretically that this patient's symptoms could be secondary to his spinal anaesthesia, there are a number of reasons to rule this out. First, the anaesthetic agent was administered with the patient in the sitting position, and the height of anaesthesia at its most profound level was never above the twelfth thoracic segment. Second, there was no evidence of arterial hypotension which might have resulted in cerebral thrombosis at any time during or immediately following anaesthesia. Third, the patient's age and general physical condition were such that even had a transitory hypotension developed, one would not anticipate the occurrence of a cerebrovascular accident. Fourth, the onset of symptoms of this type was at a time sufficiently remote from the administration of the spinal that any connection with this event is unlikely. In the event of arachnoiditis or cauda equina syndrome, however, this time relationship would not necessarily hold true.

Case 8

A 68-year-old male had a repair of ventral hernia under spinal anaesthesia. Postoperatively, he had mental confusion, developed a right hemiparesis, and was transferred to the neurosurgical service where his work-up, including a carotid angiogram, revealed a space-occupying lesion. Approximately one month postoperatively, craniotomy was performed at which time a temporal astrocytoma was found. Two months later, the patient expired from bronchopneumonia.

This case is included to demonstrate instances in which the spinal anaesthesia can be blamed for occurrences which are actually due to some extraneous cause. This brain tumour was unsuspected prior to the initial neurological work-up after the hernia repair.

Case 9

A 29-year-old male had a hemorrhoidectomy under spinal anaesthesia. Postoperatively, he complained of episodes of numbness from the dorsum of the left foot to the buttocks. He was given a complete neurological work-up first by the department of anaesthesia and then by the neurology service. No organic basis for the complaints was demonstrated and a diagnosis of conversion reaction was established. Approximately 18 months later he was readmitted and at this time he did not mention the previous complaints. He returned at this time for treatment of varicose veins.

Case 10

A 31-year-old male had a right lumbar sympathectomy performed under spinal anaesthesia for recurrent dermatophytosis with vascular insufficiency of the right leg. At the time of operation, it was noted in the chart that the lumbar puncture was performed at the level of the third and fourth lumbar interspace and was an atraumatic tap with clear cerebrospinal fluid. The patient pursued an uneventful course and was discharged nine days following surgery. Eight days later, on the seventeenth postoperative day, he was readmitted complaining of pain in the posterior aspect of his right hip and lateral aspect of the thigh and calf. At this time, a diagnosis of sciatic neuritis, mild, was made and sciatic nerve block provided relief. An X-ray of the lumbosacral spine performed at this time revealed a narrowing of the *fifth lumbar-first sacral* interspace. A diagnosis of complication of spinal anaesthesia was made by the ward physician.

Neurological or orthopedic consultations were not noted in the record. Relief was obtained on conservative management, and the patient was discharged after about two weeks of treatment with no recall scheduled.

Two years later, he was readmitted with a complaint of a non-healing right plantar ulcer. Because of the history and the fact that the present study was underway, a neurological examination was requested by the anaesthesiologist. This revealed only one abnormal finding, namely, weakness in dorsiflexion of the right foot associated with an ulcer on the plantar surface of the foot, underlying the first metatarso-phalangeal joint. Diagnosis by

the neurologist was right peroneal palsy manifested by the above deficit. Electromyogram and rheobase and chronaxie testing of the lower extremities were performed which manifested slight slowing in the right lower extremity without definitive pathology.

The patient at this time has no symptoms referable to the right lower extremity.

Inasmuch as the patient had a right lumbar sympathectomy performed it is conceivable that the pathology shown could be on the basis of this neurological procedure or pre-existing vascular disease, casting further doubt on spinal anaesthesia being the etiological factor for this patient's findings.

The 24 neurological complications accepted by us as conceivably being due to spinal anaesthesia fell into five rather broad categories as noted in Table I.

TABLE I

TOTAL NEUROLOGICAL COMPLICATIONS ENCOUNTERED IN 20,000 CASES OF SPINAL ANAESTHESIA

	1948–51 10,000 cases	1952–55 6,000 cases	1956–59 4,000 cases	Total 20,000 cases
Cerebral vascular accident within 10 days of anaesthesia	4	2	0	6
Meningitis	1	1 (died)	1	3 (2 recovery)
Persistent headache (over one week)	3	5	1	9
Chronic backache	2	0	0	2
Cardiac arrest	3 (1 recovery)	1	0	4 (1 recovery)
TOTAL	13	9	2	24
PERCENTAGE	0.13	0.15	0.05	0.12

Representative examples of these cases are as follows:

Category 1. There were six cerebrovascular accidents which occurred within 10 days of spinal anaesthesia. One such case is as follows:

A 55-year-old male had a procaine spinal (100 mg. in 5 c.c.) for a circumcision. Blood pressure had previously been recorded at 180/100 on several occasions. Immediately pre-anaesthetic, it was 112/76 with pulse of 68. During anaesthesia, it fell as low as 100/60. Approximately 12 hours post-anaesthetic, at 3:30 A.M., the patient fell to the floor. Cerebrovascular accident was diagnosed. Complete right hemiparesis ensued. Blood pressure at that time was 136/80. There was no evidence available to show that the spinal caused this CVA. The blood pressure had already fallen prior to administration of the spinal anaesthetic. The pre-anaesthetic medication could be as much to blame as the anaesthetic. The five other cerebrovascular accidents were similar.

It is established that a profound fall in blood pressure can encourage cerebral thrombosis. This results regardless of the cause of the hypotension. It is also established that spinal anaesthesia can cause hypotension. Therefore, it is quite within the realm of probability that in susceptible individuals, for example, those with cerebral arteriosclerosis, any uncorrected hypotension following spinal anaesthesia might result in a cerebral vascular accident. Whether any of the six cases in this series were so caused is not absolutely determined. It is a possibility that spinal anaesthesia played a part in the causation of these accidents, and they are therefore reported. Regional anaesthesia was really indicated in these cases.

There were three cases of meningitis with one death. These will be reported in detail.

Case 11

A 40-year-old male underwent cholecystectomy under spinal anaesthesia. Three days postoperatively he developed severe headaches when he was allowed out of bed. The headaches were less severe when he was lying down. Photophobia and sensitivity to noise accompanied them as did nausea and nuchal rigidity. Forty-five days later, the spinal fluid pressure was very low. After injecting 40 c.c. of sterile saline, spinal fluid was obtained with 207 mg. per 100 gm. of protein and 133 cells. The headaches continued for a total of 55 days at which time the cell count was 10 and protein 130 mg. per 100 gm. Follow-up examination two years later revealed no residuals. Culture and smear of cerebrospinal fluid were negative at all times. This is an anaesthetic complication. It was probably due to chemical irritation or some break in technique. Low grade infection must be considered even in view of the negative smears and cultures.

Case 12

A 56-year-old male underwent transurethral prostatic resection in April 1955 under spinal anaesthesia. Four days later he developed a low grade fever and mental confusion which gradually increased and subsequently developed nuchal rigidity and signs of meningeal irritation. In May 1955, Klebsiella was cultured from both urine and cerebrospinal fluid. The patient was treated with antibiotics and was discharged as recovered in December, 1955. This patient was a diabetic and had tertiary lues with lowered resistance to infection so that it is dubious as the the aetiology of the CNS infection, that is, whether it was systemic or direct. Lacking evidence to the contrary, however, it must be included as a possible contamination by the lumbar puncture.

Case 13

A 65-year-old male had a history of suprapubic prostatectomy for carcinoma of the prostate and stormy postoperative course. This procedure was done under general anaesthesia. Eleven months later, litholapaxy was done under spinal anaesthesia, followed in two weeks by transurethral resection of the bladder neck, likewise under spinal anaesthesia. The postoperative course following this second spinal was uneventful, and he was discharged one week later to return "on call." He came back, however, in one week without being called and was admitted for the management of clonic convulsive seizures of 1 day's duration. This condition was preceded by headaches and visual difficulties which began three days after his discharge from the hospital. At the time of readmission, a diagnosis of Jacksonian seizures, aetiology unknown, and right flaccid hemiplegia were made. X-rays showed evidence of Pineal shift. Lumbar puncture was attempted but because of the patient's restlessness was not accomplished at this time.

Approximately three weeks after the second spinal anaesthetic, a carotid angiogram and lumbar puncture were done. At this time, the cerebrospinal fluid was cloudy and had 8,000 cells, principally polymorphonuclears. The patient had a full-blown meningitis. Blood cultures at this time and two weeks later were negative although the spinal fluid culture revealed coagulase positive staphylococcus aureus. Massive antibiotic therapy was begun. A subtemporal decompression was performed. The patient also required tracheostomy. His course was progressively downhill for approximately two months until he expired.

The final anatomical diagnoses made at autopsy were:

1. encephalomalacia of the left temporoparietal lobe, massive
2. adenocarcinoma of the prostate
3. adenocarcinoma of the proximal ascending colon
4. bronchopneumonia of left upper and right middle lobes with pulmonary edema
5. adrenocortical adenoma
6. septic splenitis
7. patent foramen ovale
8. recent infarct of the right kidney

It is extremely difficult to reconstruct the aetiology of this patient's brain abscess. His symptoms began approximately 10 days following the second spinal anaesthetic and could conceivably have resulted from bacterial contamination introduced at the time of spinal anaesthesia. However, this patient also had evidence of uraemia as well as a malignancy which could very possibly have metastasized to the brain. Further possibilities are presented by the presence of the patent foramen ovale which could have resulted in a transfer of organisms from the right side of the heart to the left with embolic bacterial transmission. The negative blood cultures with positive spinal fluid cultures present some evidence that the spinal fluid infection may have been primary, but it is well known that in many instances of meningeal contamination, the blood culture may return to negative while the spinal fluid still has a high bacterial count, so that this is not in itself a conclusive finding. The presence of the renal infarction is also evidence of a generalized bacteraemia, although again it cannot be determined which came first, the bacteraemia or the meningeal infection.

Lacking evidence to the contrary, we feel that this case must be included as a possible complication of spinal anaesthesia although it is far from conclusive.

Nine cases of persistent headache of more than one week's duration are reported. These differ from the preceding cases only in degree. One such case lasted two months, another two weeks, and a third one week. Cases of headache clearing in less than one week were not considered worthy of inclusion in this study, even though they are extremely undesirable and unpleasant and are economically and scientifically spinal complications, they were not part of the subject we chose to study.

Headache which follows spinal anaesthesia is probably due to the anaesthesia if it meets certain criteria, as follows:

1. The headache is usually occipital if due to spinal.
2. There may be nuchal rigidity accompanying the headache.
3. The assumption of the supine position ordinarily affords relief with return of the headache upon assuming the erect position.
4. Ordinary analgesics such as aspirin do not completely relieve the pain.
5. A tight abdominal binder or extradural injection will frequently relieve the pain.

A 44-year-old obese male was essentially well except for haemorrhoids. He was operated upon for this condition. Postoperatively, he developed headaches which lasted for a period of about one week. From perusing the chart, no evidence of any specific treatment for the headaches was mentioned. In postoperative follow-up after hospitalization, there was no further mention of any complication.

Two cases of chronic backache are reported. Both were given diagnoses of "chronic lumbosacral strain." A typical case history follows.

A 38-year-old male had a left inguinal hernia repaired under spinal anaesthesia. He had no history or complaints relative to his back at that time. Since then he has had three admissions for treatment of chronic lumbosacral strain.

Both patients were obese and there was no evidence that the spinal anaesthetic was to blame. On the other hand, there was no evidence to show that the spinal anaesthetic was completely blameless. The good muscular relaxation afforded

by spinal anaesthesia may result in flattening of the normal lumbar curve when the patient is placed in the supine position without a small pillow or other support in the lumbosacral region. Thus, it is difficult at this time to state whether the two cases of backache were or were not due to the spinal anaesthesia. This condition can follow any anaesthetic technique that relaxes the musculature and permits abnormal stresses to occur. It is especially likely to happen when lithotomy or other abnormal positions are employed.

Cardiac arrest coincident with spinal anaesthesia occurred in four cases. Two of these, however, were moribund patients scheduled for amputation following iliac thrombosis. In these, poor judgment as to the advisability of administering any anaesthetic other than perhaps refrigeration or some form of regional block is more to be blamed than the spinal itself. The third case is somewhat more complex.

A 29-year-old male law student was given a spinal anaesthetic for laparotomy for a perforated viscus. A perforated appendix was removed, but during the procedure the spinal anaesthesia was supplemented at first with thiopentone and later with inhalation agents. As the abdominal closure was being completed cardiac arrest occurred. Resuscitation was accomplished after the heart had been stopped approximately four to five minutes. Residuals of cerebral anoxia were present for several days in the form of convulsions, animal-like cries, and so on. He then proceeded to make an otherwise uneventful recovery.

This case could certainly not be blamed entirely on the spinal. Inhalation anaesthesia and thiopentone were also employed. The discussion of this case is difficult since such a multiplicity of agents and techniques were employed. It is established that a period of respiratory obstruction and respiratory depression occurred during the general anaesthesia. It is reasonable to suppose that this with or without the spinal could be sufficient to have produced the cardiac arrest.

The fourth case resembles the one who recovered in some respects, but this time the outcome was different.

A 25-year-old male was given continuous spinal anaesthesia in April 1954 for the removal of a ruptured appendix. Two doses of 4 per cent procaine consisting of 80 and 40 mg. were given during a 50-minute period. The patient was apparently doing very well when suddenly as the abdomen was about to be closed, his pulse stopped. The patient lost consciousness and the blood pressure fell to zero and respiration ceased. Cardiac resuscitation was undertaken through a thoracotomy at once, and he resumed spontaneous cardiac rhythm and respiration but failed to regain consciousness. He expired three days later.

It is difficult, if not impossible, for us to explain the demise of this patient who was a young, otherwise healthy, manual laborer. We have no choice, however, but to include his case as a complication of spinal anaesthesia. We are at a loss to explain why prompt, efficient cardiac resuscitation was ineffectual in affording a recovery in this case.

Discussion

It will be noted that the incidence of complications in the final 4,000 cases in this series has dropped considerably from an average of 0.15 per cent in the first portion to 0.05 per cent in the last 4,000 cases. The over-all average incidence of neurological complications in the 20,000 cases in the series is exactly 0.12 per

cent. It must be especially noted that other complications (that is, cardiovascular) were not sought in making this study. It was noted, however, that in the final 4,000 cases, there were five occurrences of myocardial infarction with four deaths. These cases are not included in the statistics of this paper since it was not our province to study other than neurological complications. It is our opinion, however, that this rate of incidence compares favourably with that of vascular complications regardless of the modality of anaesthesia employed.

The type of agents that were used to produce spinal anaesthesia should be mentioned. In the vast majority (probably more than 90 per cent of the cases) Pontocaine® with 10 per cent dextrose as a solvent and weighting agent was the anaesthetic used. A few cases were performed with either Nupercaine® or procaine, but these are very few in number. In many of the anaesthetics, epinephrine was added to the other intrathecal agents. Both dextrose and epinephrine have been previously incriminated by some authors as being nerve-tissue or meningeal irritants and capable of causing neurological damage. It seems quite significant to us that there were no cases of adhesive arachnoiditis which has been pointed out by Courville[3] and others as being one of the commonest complications of spinal anaesthesia. Nor did we note any cranial nerve lesions, particularly the sixth-nerve lesion, which have been pointed out as being the commonest cranial nerve lesion.

Several alleged complications of spinal anaesthesia have been called to the attention of this department, although on closer investigation and study of the records, they were seen to have been due to extraneous causes. An example was the case of a patient in the paraplegic section of the hospital. It was reported that he had been given spinal anaesthesia and subsequently developed a spastic paraplegia which the doctor calling this to our attention felt was due to the anaesthetic. On examination of the record, however, it was determined that the onset of the paraplegia occurred some time after discharge from the hospital following an automobile accident during which the patient sustained serious internal injuries. Another such case was that of a physician who was alleged to have had paraplegia as a result of a spinal anaesthetic. On investigation, it was found that this physician had been under anticoagulant therapy for thrombophlebitis of his leg. As a result of neurological symptoms, he had a diagnostic lumbar puncture which revealed the presence of haematomyelia, which undoubtedly was the cause of his paraplegia. The patient had never received spinal anaesthesia for any condition.

These two cases typify some of the many that are called to the attention of the anaesthesiologist allegedly as neurological complications of spinal anaesthesia. We have no doubt that neurological complications can and do occur. However, we feel that the incidence of these is extremely low as compared to patients having received general anaesthesia for surgical procedures.

It is a surprising finding to us that in the third portion of our series of 20,000 cases, namely the last 4,000 from 1956 through 1959, only two complications which could have been due to spinal anaesthesia were encountered. This is even less than we anticipated or than the number encountered in the first 16,000 cases. We have no way of explaining this except chance, since our technique has

remained essentially unchanged. The principal difference between the technique used prior to 1956 and that used at the present time has been the fact that since 1956 all of the spinal anaesthetic drugs have been autoclaved prior to their injection whereas, previous to that time, the drugs were sterilized by immersion for a period of time in a solution of antiseptic agent. We do not seriously believe that this would account for the difference in the number of complications found and merely mention it in passing.

As brought out in the previous papers,[1,2] these anaesthetics were administered by a rather heterogeneous group varying widely in their training, from new residents fresh from an internship through staff anaesthesiologists to specialists of professorial rank. It is reasonably unlikely that any important complications were missed since in this hospital a large staff is employed solely for the purpose of maintaining adequate records, and, since the hospital is a 100 per cent teaching institution, this is done zealously. Follow-up of individual patients is easy to perform and is ordinarily complete, since this is a government institution and the individual recipients of care are usually quite willing to co-operate because of the involvement of compensation or pension for their problems, either real or fancied. In addition, because of the university affiliation, consultation service with the various specialties is both readily performed and well done. Third, there is no tendency on the part of the physician involved to evade the issues by minimizing complications since, should these occur, the government usually assumes financial responsibility. Therefore, the number of complications through inadequate follow-up is minimal, and should major complications occur, the likelihood of the patient returning is extremely great because they are aware of the possibility of compensation. It is possible that a few complications were missed because the patient went to another Veterans' Administration Hospital. However, this is rather unlikely. Furthermore, it is difficult to hide *sequelae* when they do occur because of the wide diversity of services involved in the hospital and the desire by each service to build up its own importance. Since it is both difficult and needless to hide complications, it can be assumed for all practical purposes that all have been reported.

While not denying that some cases could have been missed in the fashion described above, the number of cases (20,000) in which no appreciable number of complications occurred, is certainly significant in itself. During the time of this study, numerous cases of alleged complications of spinal anaesthesia were called to our attention. On closer investigation, all proved groundless. Some of these patients had general anaesthesia rather than spinal; some were due to trauma, some had no anaesthesia at all, and in spite of this, the stories were rampant that spinal anaesthesia had caused these paralyses and other neurological complications. These wild tales have harmed the reputation of an essentially safe and good technique, and in many instances caused patients to be subjected to the additional hazard of a less safe anaesthetic technique. We were amazed in this study at the frequency with which neurological complications appeared at first glance to be present, only to be shown by further investigation that they had no connection with the anaesthetic technique or administration,

as is demonstrated by the several cases which we have submitted above. Inadequate follow-up of these patients or early discharge perhaps would have been *prima facie* evidence of the spinal being at fault, while closer study disproved the original contention. Certainly, the cases as exemplified by Case 9 who exhibited findings of numbness and tingling in the left lower extremity following a spinal anaesthetic for hemorrhoidectomy are legion. Unless careful examination, as was performed on this patient, reveals that there is no organic basis for the complaint, it would definitely be blamed upon administration of the spinal. It is pertinent to this discussion to emphasize at this point that we have been rather unselective in choosing cases for spinal anaesthesia and the contraindications for this technique have been relatively few. That is, we have given spinals to patients with CNS lues and other lesions, sometimes because the diagnosis was not evident at the time of administration; yet our morbidity and mortality figures are extremely low. This does not imply that we condone or recommend this practice, but merely records the fact that we have done it and had no addition to our morbidity figures. It is also pertinent that the age of our hospital population is somewhat above that of the average hospital, comprising principally World War I and II veterans from the fourth decade up to the eighth, thus presenting a higher incidence of degenerative diseases than the average patient. Furthermore, spinal anaesthesia tends to be our technique of choice in acute abdominal emergencies, much more frequently than is the case in the average hospital.

Again we wish to emphasize the importance of an adequate neurological investigation when neurological disease or pathology follows spinal anaesthesia. This is as much to rule out other aetiological factors as to protect the patient, since it is quite evident to us, at least, that spinal anaesthesia is rarely the responsible precipitating factor.

We have also pointed out that we use dextrose, epinephrine, and catheter techniques, all of which are inclined to increase the morbidity and in spite of this our statistics are still good.

Pontocaine-dextrose is our predominant agent in most cases. Epinephrine is frequently used, and the catheter continuous spinal technique is also very frequently employed.

It is unfortunate, but true, that insurance companies, many physicians, and patients have serious doubt as to the safety of spinal anaesthesia. It is our belief that these doubts are not warranted on the basis of our group experience. We feel conversely that the intelligent employment of spinal anaesthsia may reduce morbidity. Rumour mongering may tend to prevent its use where it is bets indicated and is, therefore, a doubly vicious thing.

Summary

Twenty-four neurological complications attributable to spinal anaesthesia were found in a series of 20,000 consecutive spinal anaesthetics, an over-all incidence of 0.12 per cent. Of these 24, nine were persistent headaches lasting one week or longer with complete recovery. In three of these cases, the patients

probably should not have been subjected to spinal anaesthesia because they were moribund or nearly so prior to the administration of the anaesthetic and an error of judgment rather than an indictment of the technique should be blamed. Three cases of meningitis with two recoveries were also included because the spinal technique cannot be ruled out as the introducing factor in causing the meningitis, although there is reasonable doubt as to whether this was actually the case. Two cases of chronic backache were the remaining complications.

It is quite interesting that of the 17 neurological conditions sought in our study, only the above five occurred. There were no incidences of transverse myelitis, radiculitis, peripheral nerve lesions, foot drop, neuritides, paralyses, muscular weakness, deafness, cranial nerve lesions, persistent lower bowel and bladder dysfunction, or cauda equina syndrome observed.

Conclusions

In conclusion, it is our definite impression from the study of 20,000 consecutive spinal anaesthetics that this is the safe and recommended technique for administration of necessary anaesthesia for surgical conditions below the level of the diaphragm and where definite contraindications to this technique, neurological conditions, central nervous system lues, and so on, do not exist. Irresponsible rumour mongering and blaming of the technique for complications caused by extraneous conditions have been responsible for condemnation of spinal anaesthesia. We feel that this valuable technique has been much maligned in the past and deserves a better reputation than it now enjoys in some quarters. We shall continue to employ it as we have in the past, and we believe that it will continue to give us equally good results.

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THE SUPINE HYPOTENSIVE SYNDROME DURING CONDUCTION ANAESTHESIA FOR THE NEAR-TERM GRAVID PATIENT: CASE REPORTS

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THE NEAR-TERM GRAVID PATIENT seldom lies supine by choice, and when she does she may develop hypotension characterized by weakness, nausea, and feeling of light headedness. This fact has been well demonstrated by Goodson *et al.*,[1] who have shown the incidence of hypotension in the supine position to be as high as 11.2 per cent. Their interpretation of hypotension was a fall in systolic pressure of 30 mm. Hg or a systolic pressure below 80 mm. Hg.

Schmidt[2] proposed two possible mechanisms to explain this hypotension. The first possibility was that the gravid uterus falls backward when the patient is in the supine position, compressing the inferior vena cava, resulting in diminished venous return to the right heart, decreased cardiac output, and hence a fall in systemic pressure. The second proposition suggested "shock," secondary to stimulation of the venous plexus, behind the uterus, with resultant vasodilation and pooling in the area. The former explanation was the more acceptable, particularly in view of the increased venous pressure in the lower limbs which was demonstrated during these hypotensive episodes.

A more frequent occurrence of this syndrome during conduction anaesthesia was suggested by Kennedy *et al.*[3] who reported an incidence of hypotension of 17.7 per cent of vaginal deliveries under spinal anaesthesia (modified saddle block). Further, they pointed out that displacement of the uterus to the left (L.U.D.) and so relieving the inferior vena caval compression, was sufficient to restore systemic pressure to control levels in 93.4 per cent of the hypotensive patients. In this series the patients were in the lithotomy position and pooling of blood in the lower limbs was not a factor in the occurrence of hypotension. It would thus seem reasonable to presume that in cases of conduction anaesthesia for caesarian section, the figure of 17.7 per cent incidence of hypotension would be a conservative estimate.

To illustrate this hypotensive syndrome, the following case reports are presented.

Case 1

A 29-year-old patient, para III, gravida IV, was admitted for an elective caesarian section on January 22, 1961.

Obstetrical history. 1957, first pregnancy terminating in a spontaneous vaginal delivery at term; 1958, emergency caesarian section (under general anaesthesia) for placenta praevia; 1959, spontaneous vaginal delivery at term.

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Present history. On admission the patient was grossly overweight at 225 pounds (213 at commencement of pregnancy) and complaining of persistent pain in the region of her abdominal scar (previous section). Physical examination other than obesity was negative, blood pressure 120/80, haemoglobin 12.8 gm., urinalysis negative.

Delivery. On January 23, 1961, without premedication, the patient was taken to the O.R. and a polyethylene catheter was inserted in the epidural space at the L 4–5 interspace, in the sitting position, using a Huber tipped Tuohy needle (#17). B.P. before procedure was 120/80. Ten c.c. of 2 per cent lignocaine containing 1/200,000 adrenalin was injected through the catheter and the patient was placed in the supine position, followed by a second injection of 10 c.c. of lignocaine. Within 30 sec. the blood pressure was recorded at 60 mm. Hg systolic and the patient complained of pain over the left chest, difficulty in breathing, and a feeling of faintness. Oxygen by mask and methoxamine, 5 mg. intravenously, were administered without effect. Further increments of methoxamine were given intravenously to a total of 20 mg. The systolic pressure continued to fall and became unrecordable. At this stage, approximately 3 minutes after the patient had been placed in the supine position, because of the failure to respond to vasopressors, the supine hypotensive syndrome was considered. The patient was turned to the right lateral position, resulting in an immediate rise in systolic pressure to 120 mm. Hg.

After a short interval, the patient was again placed in the supine position, and preparation of the operative site was begun. The assumption of this position was attended by an immediate fall in the systolic pressure to 40 mm. Hg. Further attempts to carry out the operation were then abandoned and the patient was kept in the lateral position.

Later the same day, after the effects of the epidural anaesthetic had worn off, multiple blood pressure recordings were made with the patient in bed in the supine and both lateral positions. No significant change in blood pressure was noted in the various positions.

On the following day, the patient was premedicated with meperidine 50 mg., promethazine 50 mg., and atropine 0.4 mg., and returned to the O.R. one hour later. The systolic pressure in the sitting position was 110 mm. Hg, and after the patient was placed in the supine position on the O.R. table, it fell to 80 mm. Turning the patient to the left lateral resulted in a rise of pressure to 110 mm. An intravenous drip was started and levallorphan 0.5 mg. was given. After resuming the supine position, the patient was prepared and draped. General anaesthesia was rapidly induced with thiopentone 250 mg., and gallamine 120 mg., followed by intubation and maintenance with N_2O/O_2 with controlled respiration. Six and one half minutes after induction a male infant was born with an Apgar rating of 9. As soon as the uterus was emptied, the maternal systolic pressure rose immediately to 110 mm. Hg, and remained at this level.

Case 2

A 30-year-old patient, para I, gravida II, at term was brought to the delivery

room for vaginal delivery. Previous obstetrical history was normal. Present pregnancy was uneventful. Last known weight was 130. Blood pressure on admission to the delivery room was 115/60. The patient was placed in the right lateral position, and 14 c.c. 2 per cent lignocaine with 1/100,000 adrenalin was injected into the lumbar epidural space at the L 4–5 interspace through a #17 Huber tipped Tuohy needle.

Following epidural injection, the patient was placed in the lithotomy position. Over a period of 10 minutes the blood pressure fell to 75/45, with the patient appearing pale and sweating and complaining of weakness. Manual displacement of the uterus to the left would lead to an immediate pressure rise to 95/55. With uterine contractions (without displacement) the blood pressure (systolic) would rise to 95/100, then return to 75 with termination of contractions. The hypotensive episodes were accompanied by a slowing of the pulse from a previous 84/min. to 60/min.

A normal infant was delivered by low forceps 20 minutes after introduction of anaesthesia. The Apgar rating was 9. The maternal pressure immediately rose to 120/70 following delivery and remained at this level. Pressor agents were not used. Ergometrine 0.25 mg. were given intravenously 15 minutes after delivery.

Discussion

Since the supine hypotensive syndrome has been drawn to our attention, we have had eight patients exhibit the signs and symptoms of the above syndrome in the last consecutive 100 cases of vaginal delivery under epidural anaesthesia. In each instance, the systolic blood pressure fell to below 80 mm. Hg and responded to either displacement of the uterus, or the movement to the lateral position. Not one of these patients exhibited hypotension in the supine position prior to epidural anaesthesia. This is contrary to the findings of Holmes[4] who recently suggested the use of a supine hypotension test to indicate the severity of fall in blood pressure that can be expected when spinal anaesthesia is used for caesarian section.

One can readily appreciate how sympathetic paralysis in the splanchnic area would exaggerate a tendency towards hypotension due to vena caval obstruction, and it is interesting to speculate that the sudden catastrophic shock that has been reported on innumerable occasions with spinal anaesthesia in obsteterics, has perhaps been due in large measure to the latter cause. The first case report suggests that the usual methods of resuscitation with pressor agents are of no avail, whereas shifting the uterus or moving the patient to the lateral position could be life saving.

Finally, the signs and symptoms of collapse illustrated in the first case mimic those of an "accidental" total subarachnoid block, and it may be difficult, if not impossible, to differentiate. It is suggested that if severe hypotension should occur after an epidural (or spinal) block, when the patient assumes the supine position, uterine displacement might be carried out first, before assuming the cause to be a high sympathetic block, accidental or otherwise.

ACKNOWLEDGMENT

We wish to thank Dr. R. I. Merritt for his assistance and permission to publish the case histories.

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AN ANAESTHETIC SPRAY

C. J. KILDUFF, M.D.*

SINCE TOPICAL ANAESTHESIA may be used at any age, it is desirable to have a spray with interchangeable metal tubes of varying lengths. Experience with many models has indicated that the following features are desirable: the spray must stand upright and be easily seen; the base should not adhere to modern work surfaces; it should be easy to assemble, repair, and sterilize; the metal tube should be detachable and of large bore; and the only perishable part should be a standard rubber bulb.

A spray as illustrated in Figure 1 has been in use for many years by broncho-

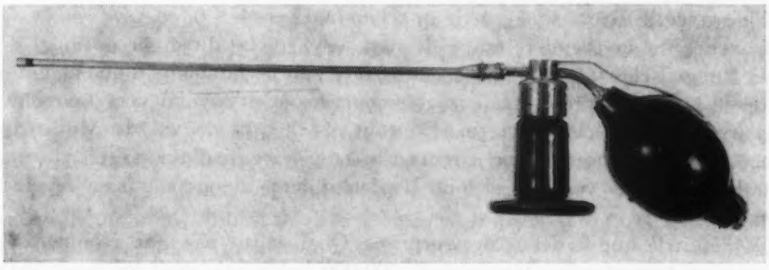

FIGURE 1

scopists for topical anaesthesia and has been very satisfactory. Its original metal tube, 32 cm. in length, was shortened to 22 cm. and proved very satisfactory for adult use. Metal tubes of varying length will now be supplied by the maker† on request for adult and paediatric use.

*From the Department of Anaesthesia, University Hospital, Saskatoon, Saskatchewan.

†Available from George P. Pilling & Son Co., 3451 Walnut St., Philadelphia 4, Pa.

UN ANESTHÉSISTE AU CONGO

RAYMOND ALLARD, M.D.*

LE PREMIER JUILLET 1960, un des plus riches pays Africains obtenait son indépendance. Le Congo Belge s'appellera désormais le Congo. La fougue, la vigueur et l'irréflexion de tout ce qui est jeune ne firent point défaut aux Congolais qui flanquèrent tous les Belges à la porte: avec le résultat que la population de 14 millions d'habitants resta sans technicien de valeur, et sans médicin. Ayant ainsi plongé son pays dans le chaos et ne sachant comment manœuvrer, le premier ministre Patrice Lumumba fit appel à l'O.N.U. C'est à la demande expresse de cette organisation mondiale, que la Croix Rouge Canadienne délégua cinq médecins et six infirmières en ces lieux troublés. Parmi eux, se trouvait un spécialiste en chirurgie thoracique, qui, sans anesthésiste, se trouvait réduit à l'impuissance. Et c'est ainsi que je m'acheminai vers le Congo.

Bruxelles fut la première étape de mon voyage. Le directeur national de la Croix Rouge Belge y était à ma rencontre et me fit les honneurs d'une magnifique visite de la ville. Après cette agréable journée, je m'envolai vers Léopoldville où j'arrivai le lendemain matin. En tout, 14 heures de vol de Montréal au Congo. Le premier homme que je rencontre à ma descente d'avion est le chirurgien pour lequel j'étais venu de si loin. Il prenait mon avion pour s'en revenir au Canada.

Ce n'était là que le début des surprises. Quel ne fut pas mon étonnement en découvrant Léopoldville. Une cité de 500,000 habitants, dont les constructions de style moderne, serpentées de larges rues pavées d'asphalte et bordées d'arbres multicolores, et d'une propreté frappante, me firent échapper mes premiers mots: "Est-ce cela un pays sous-développé!" Comme mon arrivée coïncidait avec la fin de semaine, et qu'en fin de semaine au Congo, tout s'arrête, l'on m'installa dans un hôtel jusqu'au lundi. Cela me permis de me remettre de mes émotions, et de retrouver ma forme physique nécessaire à un autre voyage à l'intérieur du pays, afin de rejoindre le groupe canadien à Coquilatville. Mais voilà que le lundi, l'on m'annonce qu'il y a une université à Léopoldville, et que l'Organisation Mondiale de la Santé aimerait m'y garder. Que diable! Une université en ce pays! A peu près au même temps, quatre infirmières canadiennes sont ramenées de Coquilatville à Léopoldville, et placées sous ma charge. Deux resteront au dispensaire nouvellement ouvert pour les gens de l'O.N.U., à Léopoldville, tandis que les deux autres seront avec moi à l'Université. Comme cette dernière est située à 15 milles de la ville, une Ford 56 est mise à ma disposition pour mes déplacements. C'est dans cette voiture qu'un jour, un garagiste versa 14 gallons d'eau au lieu de l'essence.

L'Université Lovanium, comme le reste, est de plus modernes. Sise sur un

*Chef Résident en anesthésie, Hôpital Royal Victoria, Montréal, P.Q.

plateau, elle domine Léopoldville. En son sein, nous y trouvons la majorité des facultés, avec de plus un quartier résidentiel pour les professeurs. C'est dans une de ces villas abandonnées par les Belges qu'on me logera. Tout y était resté intact, même la réserve de vin. L'hôpital de 300 lits comportait tout le matériel anesthésique voulu pour travailler: trois Marretts, une Boyle, O_2, N_2O, éther, trilène, fluothane, penthotal, démérol, curare, laryngoscope, tubes endotrachéaux, tout sauf le C_3H_6.

Parti du Canada pour aller dans la brousse, ces présentes conditions étaient très acceptables. Il ne restait donc plus qu'à se mettre au travail. Les premiers jours, je fus débordé; il était bien vrai que les deux chirurgiens Belges, résistants, m'attendaient. Tout de même, je m'en tirai assez bien, avec l'aide d'un finissant en médecine, un Congolais, lequel cependant après quatre jours ne se montra plus, et pour cause: il avait été promu commissaire général de la santé dans le nouveau gouvernement Mobutu. C'était le seul Congolais dont les connaissances médicales étaient assez élaborées pour prendre charge d'un tel poste. Par la suite, j'héritai de trois infirmiers avec mission d'en faire des anesthésistes. Je leur donnai trois cours théoriques par semaine, en plus des leçons pratiques de chaque jour. Vraiment, ils furent épatants et me permirent de faire beaucoup d'ouvrage en peu de temps. Je n'ai pas la prétention d'en avoir fait des anesthésistes, mais je crois que sous surveillance, ils seront en mesure de rendre de grands services. Ils ont au moins appris que celui qui endort un malade, a la vie de ce malade entre les mains. Un jour, m'arrive un paraplégique en dénutrition, dont la cause des malaises était une t.b. cervicale. Le chirurgien avait décidé de tenter une greffe d'Albee à ce niveau. (Il n'était pas question de préparer les malades à l'opération, tout était désorganisé, et le personnel rare. Les malades étaient tout simplement conduits à la salle d'opération sans plus de frais qu'une prémédication.) Celui-ci avait reçu démérol 50 et atropine 0.4. Donc, après avoir examiné le cœur, les poumons et pris la T.A., et constaté que tout était normal cliniquement, je lui donne 100 mg. de penthotal, et installe un système semi fermé, N_2O, O_2. Un de mes élèves ventile le malade qui reçoit 50 mg. de succinylcholine. Un tube numéro 9 est passé mais au moment de gonfler le ballonnet, je suis frappé par la couleur anormale de la langue du malade. C'était le drame, le classique arrêt cardiaque. Le thorax est ouvert immédiatement et 30 secondes de massage sont suffisantes à remettre le cœur en marche. L'on s'empresse de me dire que c'est la première ressuscitation réussie à Lovanium. Dix jours plus tard, le malade est à nouveau sur la table d'opération et cette fois, la greffe est faite sans incident. Deux moins après l'opération, ce type peut mouvoir ses membres et se porte très bien. Leçon pour tout le monde, mais qui a fait comprendre mes élèves, qui à partir de ce moment m'appelèrent: "Professeur . . . !"

Au Congo, l'Université ouvre ses portes à la fin d'Octobre. Plusieurs professeurs, des vrais ceux-là, revinrent, et parmi eux environs 18 médecins Belges, dont un chirurgien thoracique. L'ouvrage devint alors beaucoup plus intéressant. Au total durant mon séjour de trois mois, j'ai anesthésié 290 malades; un peu de tout, de l'ouverture d'abcès, à la gastrectomie et la lobectomie. J'ai utilisé

différentes techniques anesthésiques, allant de l'éther pur au goutte à goutte d'anectine avec N_2O et O_2. J'en ai conclu que le Congolais est très sensible aux médicaments de toute sortes. Le malade qui a reçu 100 mg. de démérol en prémédication devient un problème anesthésique; une induction de 100 mg. de pentothal seulement, le plonge dans un troisième plan chirurgical. Par contre celui qui n'est pas prémédiqué, se manipule très facilement mais atteint aussi un plan chirurgical de façon rapide. J'ai cherché à comprendre le pourquoi de cette susceptibilité particulière, sans pouvoir rien trouver de satisfaisant, si ce n'est le psychisme particulier de ces malades. En effet, un Congolais décidé à se faire soigner, est un être détendu, confiant, et s'abandonnant totalement à son médecin. J'ai la conviction que ces gens doivent être très faciles à hypnotiser. Ce qui est le plus surprenant, c'est que ces constatations s'observent même chez les enfants. Les 40 cas de pédiatrie que j'ai eu à endormir n'ont reçu en prémédication que de l'atropine, et l'induction au masque a toujours été très facile.

La vie sociale à l'université était assez agréable. Nous avions un club à notre disposition où trois fois par semaine il y avait cinéma. Les sports tenaient une grande partie de nos divertissements, surtout le tennis et la natation. Comme membre de la Croix Rouge, je pouvais aller à peu près n'importe où. L'uniforme nous faisant respecter de tous. Personnellement, je n'ai en aucune difficulté et j'ai pu visiter les environs de Léopoldville sans être mollesté. Je dois ajouter cependant, que cette liberté de mouvement était dûe à la Croix Rouge Canadienne. En effet, parmi la grande variété de médecins que j'y ai rencontrés, nous étions les seuls à posséder un uniforme vraiment distinct, et qui ne prêtait pas à équivoque; ce qui je crois m'a évité bien des ennuis. Car lorsqu'un soldat ou un policier Congolais se décidait arrêter les gens, pour fin d'identification, tous les autres faisaient de même, de telle sorte que durant la même journée, nous pouvions être arrêtés une dizaine de fois. Ces gens ne savaient pas pourquoi ils nous arrêtaint, mais tout de même ils le faisaient, et à leur façon: le canon de leur fusil était la première chose qui apparaissait dans il voiture, et nous arrivait sur le nez ou le thorax. Quand on sait que le Congolais est un enfant nerveux, cela rend la chose encore mois agréable. Toutefois, découvrant vite notre identité, ils s'empressaient de retirer leur "joujou" et de faire le salut militaire.

Je remercie donc la Croix Rouge Canadienne de m'avoir fourni l'arme la plus efficace nécessaire au Congo, la CROIX ROUGE. Je lui suis reconnaissant aussi de m'avoir donné (sous sa protection) l'opportunité d'enrichir ma vie d'une si belle expérience.

LETTERS TO THE EDITOR

Department of Anaesthesia,
Westminster Hospital,
London, Ontario,
March 7, 1961.

SIR:

Dr. Douglas MacDonald's article, "An Anaesthetic Record," was very interesting, but I would like to plead for a return to simplicity. The teaching hospital has a large volume of work, and it is possible in a short period of time to arrive at statistically acceptable conclusions. The I.B.M. anaesthetic records, with their wealth of detail and symbols, are then justified.

In the majority of hospitals, the analysis of records and publication of conclusions must take second rather than equal place with good patient care. The anaesthetist has charge of treatment for a brief, acute period in the patient's illness. He must record such treatment in detail, but in such a clear and concise way that other physicians may look back at the chart during the postoperative period and know at a glance what the anaesthetist did and thought.

To this end the record sheet should have the minimum of printed words. If less space is taken to print drugs, techniques, and relatively infrequent preanaesthetic consideration, such as "cortisone," "full stomach," and more space is available to record correctly, without abbreviations, the anaesthetist's preanaesthetic evaluation and the actual anaesthetic agents and techniques employed. There should be adequate, but uncluttered space to record the fluid therapy, any problems encountered, and thoughts on why they were encountered. This is important to our colleagues who are assessing postoperative course in relation to an anaesthetic complication.

There is a tendency to design anaesthetic records so that every possible event in every possible operation can be ticked off on one sheet. The time has come to design a basic simple sheet for the average case, and a second supplementary sheet which can be used for recording the extra details of managament required in, say, chest surgery, cardiovascular surgery, and major abdominal procedures. Each record would then be comprehensible to all whom it might concern, present and future.

HAROLD CAMERON, M.D.

Nuffield Department of Anaesthetics,
Radcliffe Infirmary,
Oxford.

SIR:

With regard to my recent letter concerning the effects of nitrous oxide, I am afraid that both my outlook and my intentions may have been misinterpreted. May I therefore write a few more words on what I consider to be a most important research problem.

To Professor Robson and Dr. Burns I apparently gave the impression of being offended that one should criticise the "obvious" (although this word was not used in my letter). If I indeed gave this impression I should like to correct it without delay: I am very willing to see anything criticised, although I may not be convinced by the criticism. Further, Professor Robson and Dr. Burns took exception to my remarks because they felt that I was criticising them for not being "content to explain analgesia by saying one has no awareness of pain because one is thinking of other things"; this again, I think, is a misrepresentation of my standpoint. I made no criticism of the work of Professor Robson's team in this context; in the relevant part of my letter I suggested that impaired concentration should be taken into account in the assessment of analgesia under the experimental conditions of which I have personal experience.

Most important of all, in their reply to my letter Professor Robson and Dr. Burns several times asserted their belief that it is "worth while" questioning subjective experience and common sense, their implication being that I hold a different view. In fact their statement is one with which I naturally agree: it epitomises a problem which has exercised the minds of psychologists since the time of Wundt, to say nothing of the controversies that have raged around philosophical idealism. The whole history of psychology, from the earliest days of Freud and Jung, has been interwoven with complaints like Professor Robson's —that "the commonly accepted methods in medical research" are being "attacked." Yet few people seriously doubt that introspection and psycho-analysis have made valuable contributions to our understanding of the mind, despite their "unscientific" and sometimes, dare I say, "common sense" approach.

The intention of my letter was not to advance a comprehensive theory in opposition to Professor Robson and his colleagues, but rather to suggest some of the limitations of the "commonly accepted methods," and to contribute some personal observations arising from a different, and perhaps neglected, approach to the same problem; for in the study of metal preformance, I hold Lord Cohen's view that "worthy and relevant information from any source is equally precious."

J. PARKHOUSE

BOOK REVIEW

FLOW PROPERTIES OF BLOOD AND OTHER BIOLOGICAL SYSTEMS. By A. L. Copley and G. Stainsby. New York: Pergamon Press Inc. 1960. $12.50.

This book contains the proceedings of an informal discussion convened by the Faraday Society (Colloid and Biophysics Committee) and the British Society of Rheology. Commenting upon the summaries of the papers presented, Professor P. R. Allison states in the opening address, "not all of us would understand all of the papers all of the time." To anaesthetists thumbing through the book, especially should it first open at formula-filled page 76, this would seem somewhat of an understatement; such was this reader's opinion. However, in Part III the rheological aspects of bronchial mucus, hyaluronidase, and skeletal muscle are discussed. Starting from here one's appetite is whetted and a fuller understanding of this intriguing science is desired. Truly a book of academic nature, it is an intellectual stimulant. Those involved in research problems in anaesthesia may well find within these pages information of great import.

J.H.K.

NEWS LETTER

British Oxygen Canada Prize, 1961

The British Oxygen Canada Prize for 1961 was divided equally between Dr. R. A. Millar of McGill University for a study entitled "Sympatho-Adrenal Responses During General Anaesthesia in the Dog and Man" and Dr. Lewis W. Hersey of the University of Western Ontario for a study entitled "Central Effects of Five Muscle Relaxants."

Quebec Division

Medical economics headline the Quebec News Letter of the Canadian Anaesthetists' Society. The Hospitalization Insurance law voted at top speed proves how fast socialization can move. With this in mind, the committee on medical economics of the Quebec Division composed of Drs. Roger Gagnon and J. B. I. Sutherland swung into action. Following several meetings with medical insurance companies, a scale of anaesthetic fees was drawn up.

Meanwhile, the Quebec College of Physicians and Surgeons is also studying a scale of fees covering the various specialties, in view of the possibility of a comprehensive medical service plan.

Recently a delegation of our Division, headed by Dr. Leon Longtin, the newly-elected chairman of the Quebec Division, and comprising Drs. Georges Cousineau, Louis Lamoureux, Marius Dubeau, J. B. I. Sutherland, and Roger Gagnon met with the College. The College requested that a regular schedule of fees be submitted to them.

It was decided that the scale of fees should be based on the nature of the procedure, rather than on a time basis, or as a fraction of the surgical fee.

The College has agreed to meet with a representative of the Workmen's Compensation Board to re-evaluate the present scale of fees.

Anaesthesia has been a recognized specialty in Quebec only since 1948 but, due to the drive of its members, it is now worthy of a place beside other specialties.

In February, Dr. Richard Gilbert, Chairman of the Department of Anaesthesia McGill University, was guest lecturer at the University of Minnesota. He also represented the Quebec Division of the Canadian Anaesthetists' Society at the opening of the Ralph Knight Anesthesia Laboratory.

This spring the Montreal anaesthetists were treated to a lecture by Dr. David Little of Hartford, Conn. Dr. Little gave an authoritative talk on the present status of hypotensive techniques in anaesthesia.

Dr. Francis Foldes of Pittsburg lectured to the same group on muscle relaxants.

Dr. Merel Harmel was the final guest speaker of the session. He focused our attention on the importance of pH changes in anaesthesia.

Dr. R. A. Millar of the Department of Anaesthesia of the Montreal Neurological Institute visited Dr. Harmel's Department of Anaesthesiology at the Down State

University of New York. He addressed the Anaesthetic Division of the King's County Medical Society on the subject of Carbon Dioxide and Acid-Base Balance.

Early this summer Dr. H. T. Davenport of the Department of Anaesthesia of the Montreal Children's Hospital will begin a sabbatical year in the Department of Anaesthesia at the Christian College of Vellore of Madras University. Dr. Roy Simpson, who is presently a member of Sir Robert McIntosh's department in Oxford, will spend a year in Dr. Davenport's department.

Division du Québec

Le point de vue économique prend d'emblée les manchettes des nouvelles dans la division du Québec de la Société Canadienne des Anesthésistes.

La loi d'assurance-hospitalisation passée en un temps record a démontré à quelle vitesse pouvait procéder la socialisation dans tous les domaines. L'assurance-santé peut maintenant survenir en aucun temps.

Dans cet esprit, le comité d'économie médicale de notre division, présidé par le docteur Roger Gagnon, secondé par le docteur J. B. I. Sutherland, a continué son travail intense. Après les différents contacts effectués avec les diverses compagnies d'assurance-maladie, le travail a été poursuivi en vue du parachèvement d'une échelle d'honoraires professionnels dans la spécialité pour notre division.

Le Collège des Médecins et Chirurgiens de la province, de son côté, en prévision de l'assurance-santé possible, est à préparer une échelle d'honoraires pour les diverses spécialités. Cette échelle serait acceptable tant pour un plan d'assurance-service que pour l'honoraire du médecin-spécialiste.

De part et d'autre le chemin était parcouru, une rencontre s'imposait. Une représentation de notre division, présidée par le nouveau président, le docteur Léon Longtin, et composée des docteurs Georges Cousineau, Louis Lamoureux, Marius Dubeau, J. B. I. Sutherland et Roger Gagnon, répondait donc à l'invitation du Collège en date des 3 et 11 avril dernier.

Au cours de ces deux assemblées, des plus amicales d'ailleurs, une certaine modification à la présente échelle d'honoraires a été apportée pour la rendre acceptable à un plan d'assurance-service.

Le Collège demandait également qu'on lui fasse parvenir la cédule régulière de nos honoraires.

Le principe d'honoraires basés plutôt sur la nature de l'acte médical spécialisé que sur la durée du service, ou sur une proportion des honoraires chirurgicaux, était enfin accepté. Le Collège accepte également de présider à une entrevue avec la Commission des Accidents du Travail pour une révision des honoraires actuels. Un mémoire détaillé doit paraître prochainement du travail accompli et des principes évoqués à l'occasion de ces assemblées avec le Collège.

La spécialité d'anesthésie, reconnue comme telle dans le Québec depuis 1948 seulement, a réussi, grâce à la valeur et à l'esprit d'organisation de ses membres, de prendre place auprès des autres spécialités beaucoup plus âgées pour attendre avec elles les développements possibles et prochains, qui pourraient bien être définitifs pour la profession médicale dans son ensemble.

En février dernier, le docteur Richard Gilbert, chef du département d'anesthésie à l'Université McGill, était le conférencier invité à l'Université du Minnesota. Il a aussi représenté la Division du Québec de la Société Canadienne des Anesthésistes à l'ouverture du Ralph Knight Anaesthesia Laboratory.

Ce printemps, les anesthésistes de Montréal ont assité à une conférence du docteur David Little de Hartford, Conn. Le docteur Little parla alors de l'état présente des techniques d'hypotension contrôlée en anesthésie.

Le docteur Francis Foldes de Pittsburg donna une conférence au même groupe sur les relaxants musculaires.

Le docteur Merel Harmel a été le dernier conférencier invité de la session. Il attira notre attention sur l'importance des changements de pH en anesthésie.

Le docteur R. A. Millar, du service d'anesthésie de l'Institut Neurologique de Montréal, a par la suite visité le service d'Anesthésie du docteur Harmel à l'Université Down State de New York. Il adressa la parole à la Division d'Anesthésie de la Société Médicale du comté de King, abordant le sujet du CO_2 et de l'équilibre acide-base.

Au cours de l'été, le docteur H. T. Davenport, du Service d'Anesthésie du Montreal Children's Hospital commencera une année de congé universitaire au cours de laquelle il poursuivra des études d'Anesthésie au Christian College of Vellore de l'Université de Madras.

Le docteur Roy Simpson qui est présentement membre du service de Sir Robert McIntosh à Oxford, passera un an dans le service du docteur Davenport.

BRITISH OXYGEN CANADA PRIZE

BRITISH OXYGEN CANADA LIMITED have made available the sum of $1,000 annually for the prize to be awarded by the Canadian Anaesthetists' Society for the best original work in Anaesthesia completed in Canada during the year preceding the award. The second such prize will be awarded at the time of the Annual Meeting of the Canadian Anaesthetists' Society in 1962. The following regulations apply:

Qualifications

(1) Applicant must be a resident in training in Anaesthesia or a practising anaesthetist.

(2) The study must be carried out in a Canadian Hospital or University, and must have been completed during the previous 12 months.

(3) The study submitted may be of a basic or clinical nature.

Submission and Selection

(1) Applicant's study is to be submitted in quadruplicate to the Secretary, Canadian Anaesthetists' Society, *prior to December 31st, 1961*. The paper should *not* contain the name of the author, which will be communicated to the Secretary in a covering letter only.

(2) Where more than one person has participated in the work reported, the application for the prize must be made in the name of one of them only.

(3) Each applicant for the British Oxygen Canada Prize must be prepared to present such report in the programme of the Annual Meeting of the Canadian Anaesthetists' Society. The right of publication of all reports submitted in application for the prize is reserved to the Canadian Anaesthetists' Society Journal subject to acceptance by the Editor.

(4) Four (4) referees will be appointed by the Executive of the Canadian Anaesthetists' Society from departments of Anaesthesia in Canadian Universities. Not more than one referee shall be chosen from any one University.

(5) In the event of two (2) applicants submitting work judged by the referees to be of equal merit, the award may be divided at the discretion of the referees.

(6) If in the opinion of the referees the studies submitted do not warrant the award being made in any year, the prize will be deferred.

MEETINGS

ONTARIO DIVISION
CANADIAN ANAESTHETISTS' SOCIETY
Kingston, Ontario
October 6–7, 1961

CANADIAN ANAESTHETISTS' SOCIETY ANNUAL MEETING
Seigniory Club, Montebello, P.Q.
May 14–17, 1962

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Vienna, Austria
September 3–8, 1962

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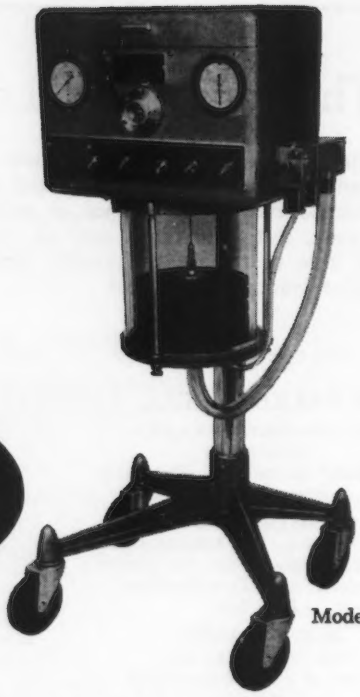

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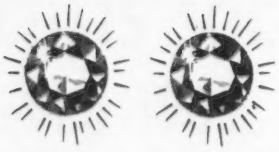

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Bibliography: 1. Javid, M.; Settlage, P., and Monfore, T.: Surgical Forum *7*:528, 1957. 2. Javid, M., and Settlage, P.: Tr. Am. Neurol. A. 1957, *82*:151. 3. Javid, M.: Surg. Clin. North Am. *38*:907 (Aug.) 1958. 4. Taheri, Z. E.: J. Internat. Coll. Surgeons *32*:389 (Oct.) 1959. 5. Stubbs, J., and Pennybacker, J.: Lancet *1*:1094, 1960. 6. Katz, R. A.: New England J. Med. *262*:870 (April 28) 1960.

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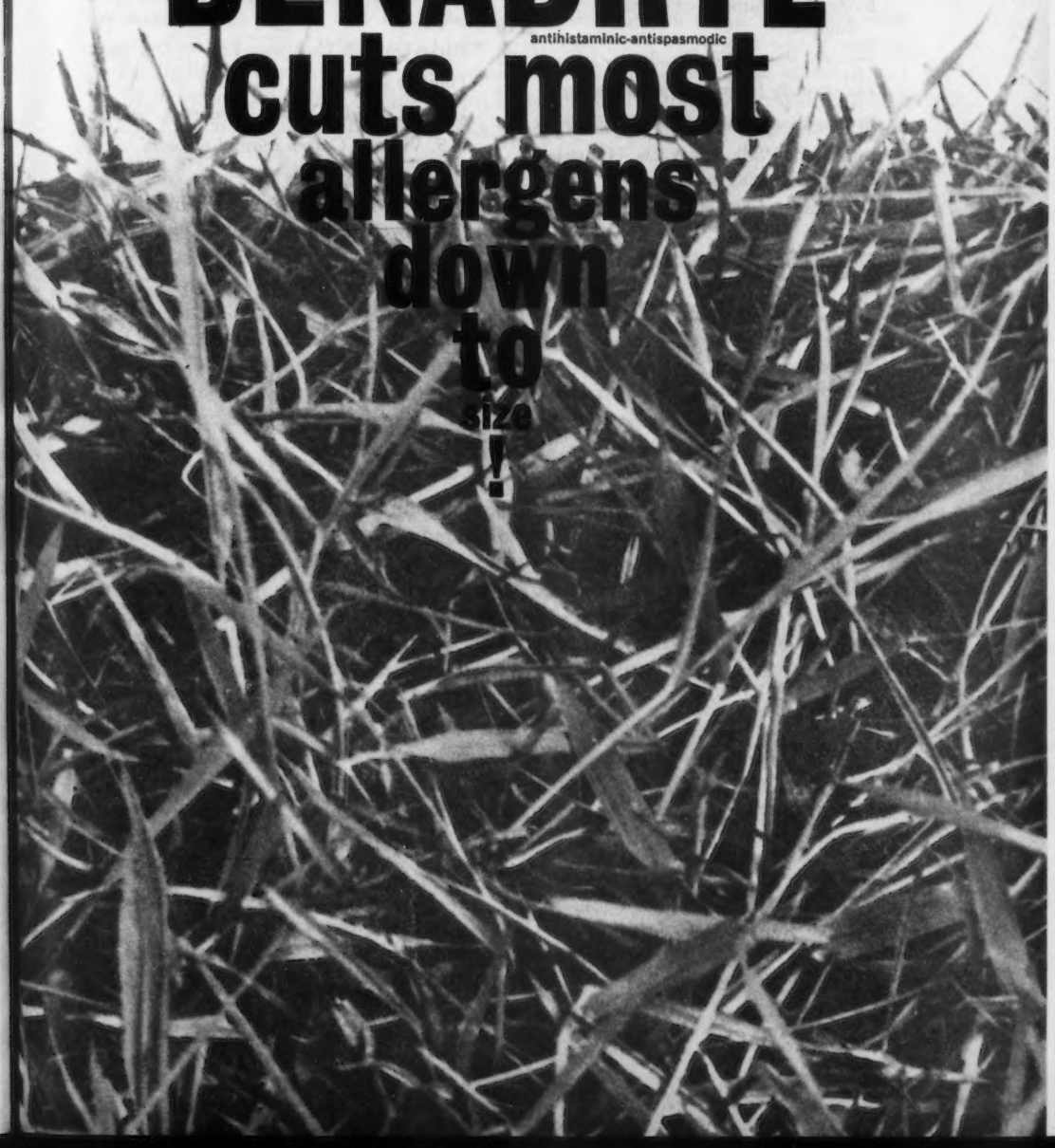

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THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

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